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 for human use, prepared in cell cultures (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 international standard and the NIH test

For a list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder and solvent for suspension for injection in prefilled syringe
Uniform white-coloured powder

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, as a primary vaccination or as a booster dose.

Pre-exposure prevention of rabies (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 a diagnostic, research or production laboratory working with the rabies virus, should be vaccinated. A serological test is recommended every 6 months (see section 4.4).
Pre-exposure vaccination should also be considered for subjects at frequent risk of exposure to the rabies virus, such as:

- veterinarians, veterinarians' assistants, and animal handlers
- those who, either by profession or leisure activity, are in contact with species such as dogs, cats, skunks, raccoons, bats or other species likely to have rabies. Examples of such people are gamekeepers, hunters, forestry workers, speleologists and taxidermists.
- adults and children living or travelling in enzootic areas.

A serological test can be performed every 2 to 3 years for those subject to discontinuous exposure.
In areas where the enzootic level of rabies is low, veterinarians and their assistants (including students), animal handlers and wildlife officers (gamekeepers) are considered to be at occasional risk of exposure and should receive a primary vaccination against rabies.
Serological tests for rabies antibodies should be performed at regular intervals in accordance with the subject's risk of exposure.

Systematic booster injections should be administered in accordance with the subject's risk of exposure. The frequency of booster injections is described in section 4.2.

Post-exposure prevention of rabies (Post-exposure vaccination):
Upon the slightest risk of rabies contamination, post-exposure vaccination should be performed as soon as possible. In some countries, vaccination must be performed in a specialized rabies treatment centre.
Post-exposure treatment includes local, non-specific treatment of the injury, passive immunisation with rabies immunoglobulins (RIGs) and vaccination, depending on the type of injury and the status of the animal (see Tables 1 and 2).

Table 1: Course of action depending on the status 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 treatment 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 treatment centre for treatment.	Treatment[(b)] is discontinued if the analyses are negative or, otherwise, continued
Live animal Non-suspect circumstances	Place under veterinary supervision[(a)]	Decision to delay rabies treatment	Treatment[(b)] is adapted according to the results of veterinary supervision of the animal
Suspect circumstances	Place under veterinary supervision[(a)]	To be taken to a rabies treatment centre for treatment.	Treatment[(b)] is discontinued if veterinary supervision invalidates the initial doubts, or, otherwise, continued

(a) In France, veterinary supervision includes 3 certificates, drawn up on 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 severity of the wound: see Table below.

Table 2: WHO guidelines on post-exposure treatment depending on wound severity

Category of severity	Type of contact with a wild[(a)] or domestic animal presumed or confirmed rabid or an animal that cannot be placed under supervision	Recommended treatment
I	Touching or feeding of animals Licks on intact skin	None, if a reliable case history can be obtained
II	Nibbling of uncovered skin Minor scratches or abrasions without bleeding Licks on broken skin	Administer vaccine immediately[(b)]
III	Single or multiple transdermal bites or scratches Contamination of mucous membrane with saliva (i.e., licks)	Administer rabies immunoglobulins and vaccine immediately[(b)]

(a) Contact with rodents, rabbits, or hares does not normally necessitate specific rabies treatment.

(b) Discontinue treatment if the animal is in good health after 10 days of observation (for cats and dogs) or if, after the animal has been euthanized, the results of the search for rabies by the appropriate laboratory techniques are negative.

4.2 Posology and method of administration

Posology

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

The vaccination schedule should be adapted in accordance with the circumstances of vaccination and the subject's rabies immune status.

4.2.1 Pre-exposure vaccination

Three doses of VERORAB (0.5 ml) should be administered on D0, D7 and D28 or D21.

Booster injection after pre-exposure vaccination

A VERORAB booster injection (0.5 ml) should be administered one year after primary vaccination, followed by a booster injection every 5 years (see Table 3).

Table 3: Recommendations for primary vaccination and booster injections

Primary vaccination	**3 Injections**	**D0, D7 and D28***
1st booster injection	**1 year later**	
Subsequent booster injections	**Every five years**	

* The D28 injection can be administered on D21

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)).

4.2.2 Post-exposure vaccination:

First aid: local treatment of the wound

All bites and scratches should be immediately flushed out and washed with soap or detergent. Doing so can enable efficient elimination of the rabies virus at the infection site.

A 70 % alcohol solution, a tincture (or solution) of iodine, or a 0.1 % quaternary ammonia solution can then be applied (provided that there are no remaining traces of soap, because these two products neutralize each other).

Depending on the severity of the injuries, rabies immunoglobulins (RIGs) may have to be administered in association with the vaccine. In this case, refer to the instructions for use in the RIG package leaflet.

If necessary, treatment can be supplemented by the administration of a tetanus prophylaxis treatment and/or antibiotherapy.

Fully immunised subjects

Two booster doses of VERORAB (0.5 ml) should be administered on D0 and D3.

Administration of rabies immunoglobulins (RIGs) is not necessary and should not be performed in this case, since booster injection is always followed by an anamnestic response.

Previously immunised subjects should be able to document the following:

- Full pre- or post-exposure rabies vaccination, by a cell culture vaccine or
- A documented rabies antibody titre ≥ 0.5 IU/ml

In case of doubt, if the booster injection was administered more than 5 years ago, or in the case of incomplete vaccination, the patient should not be considered to be completely immunised, and complete post-exposure treatment should be initiated

Table 4: Recommendations for post-exposure rabies vaccination depending on previous vaccinations

Vaccination within the last 5 years (with a cell culture VERORAB vaccine)	2 injections: D0 and D3
Vaccination more than 5 years ago or incomplete vaccination	Essen regimen: 5 injections: D0, D3, D7, D14 and D28, with RIGs administration if necessary Zagreb regimen: 2 doses on D0, 1 dose on D7 and D21, with RIGs administration if necessary

Non-immunised subjects

Essen regimen
Five doses of VERORAB (0.5 ml) administered on D0, D3, D7, D14 and D28.

or

Zagreb regimen (schedule 2-1-1)
Administration of four 0.5 ml doses of VERORAB: one dose administered in the right deltoid region and one dose administered in the left deltoid region on D0, then one dose in the deltoid region on D7 and D21.

Whatever the regimen used, rabies immunoglobulins (RIGs) should be administered concomitantly with the first injection in the case of a severe injury (category III, according to the WHO rabies risk classification). Equine and human immunoglobulins can be used with VERORAB.

The internationally recognized RIG posology is as follows:

Human rabies immunoglobulins: 20 IU/kg of body weight

Equine rabies immunoglobulins: 40 IU/kg of body weight

Because RIGs may partially inhibit active antibody production, no more than the recommended dose should be administered.

The vaccine should be injected contralaterally to the RIG administration sites.

In enzootic rabies areas, the administration of two vaccine injections on D0 may be justified, e.g. in the case of lesions that are extremely severe or located near the nervous system, or when the subject is immunodeficient or did not come in for a medical consultation immediately after exposure.

Method of administration

VERORAB is administered by the intramuscular route only, into the deltoid area in adults or the anterolateral aspect of the thigh in infants and toddlers (see also sections 4.4 and 6.6).

If using the Zagreb regimen, one dose should be administered in each deltoid region (left and right) in adults on D0, then one dose on D7 and D21.

4.3 Contraindications

4.3.1 Pre-exposure

The usual contraindications to any vaccination apply: in the case of fever or acute disease, vaccination should be postponed.
Known hypersensitivity to the active substance, to one of the excipients, to polymyxine B, to streptomycin, or to neomycin.
In all cases, the risk/benefit ratio should be assessed.

4.3.2 Post-exposure

Because rabies is always fatal, there is no contraindication to post-exposure vaccination.

4.4 Special warnings and precautions for use

Injection-schedule recommendations should be followed scrupulously. Particularly in the case of post-exposure vaccination, it is imperative to take into account the status of the animal, the circumstances surrounding contact with the animal, and the nature of the wound when administering the treatment (see section 4.2).

As is the case with all injectable vaccines, it is recommended to have appropriate medical treatment readily available in case of anaphylactic reaction immediately after vaccination, particularly a post-exposure vaccination in subjects with a known hypersensitivity to polymyxine B, to streptomycin, or to neomycin.

Do not inject by the intravascular route. Ensure that the needle does not penetrate a blood vessel before vaccine injection.

VERORAB must not be administered by the subcutaneous route. VERORAB must not be injected into the gluteal area, because weaker levels of neutralising antibodies have been observed when this area is used.

Regular serological tests are necessary. These serological tests are performed by verifying the complete neutralisation of a test virus, by the RFFIT method (Rapid Fluorescent Focus Inhibition Test). This test should be done every 6 months for people at permanent risk of exposure, and every 2 to 3 years after each booster injection for subjects at discontinuous risk of exposure. If the antibody level is under that considered to be protective, i.e., 0.5IU/ml (RFFIT), a booster injection should be administered.

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 of their antibody level should be done 2 to 4 weeks after vaccination. If the antibody level is lower than that considered to be protective, i.e., 0.5 IU/ml (RFFIT), an additional injection should be administered.

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 $\leq$ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

4.5 Interactions with other medicinal products and other forms of interaction

Corticosteroids and other immunosuppressive treatments can interfere with the production of antibodies and lead to the failure of the vaccination (see section 4.4).

Immunoglobulins must be administered at a different site from that of the vaccine (the contralateral side) (see section 6.2).

4.6 Pregnancy and lactation

Pregnancy

There are no reliable data concerning animal teratogenicity.
Clinical use of the vaccine during a limited number of pregnancies to date has revealed no particular toxic or foetotoxic effect. Nonetheless, additional studies are necessary to evaluate the consequences of exposure during pregnancy.
Because of the severity of the disease, the vaccination schedule should not be modified as a result of pregnancy.

Lactation

This vaccine may be used during Lactation.

4.7 Effects on ability to drive and use machines

There have been frequent reports of post-vaccination dizziness. This side effect can temporarily affect ability to drive and use machines.

4.8 Undesirable effects

Minor local reactions: pain, erythema, oedema, pruritus and induration at the injection site
General reactions: moderate fever, shivering, malaise, asthenia, headaches, dizziness, arthralgia, myalgia, gastro-intestinal disorders. (nausea, abdominal pain)
Exceptional cases of anaphylactoid reaction, urticaria, rash.

Apnoea in very premature infants (born $\leq$ 28 weeks of gestation)(see section 4.4).

4.9 Overdose

No case of overdose has been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: RABIES VACCINES, ATC Code: J07B G

Injection of VERORAB leads to a specific immune response. Neutralisation of the rabies virus by rabies antibodies plays a major role in the protection.

Because the disease is fatal, a controlled efficacy study is not possible. Nonetheless, a rabies antibody titre $\geq$0.5 IU/ml (measured by RFFIT) is considered by the WHO to be indicative of protection against the disease.

Administering human rabies immunoglobulin (HRIG) or equine rabies immunoglobulin (ERIG) at the same time as the injecting the first 2 antirabies vaccine doses while using the Zagreb regimen may induce a mild decrease in the mean titre of neutralising antibodies.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder: maltose, human albumin
Solvent: sodium chloride, water for injections

6.2 Incompatibilities

Rabies immunoglobulins and vaccines should never be combined in the same syringe or injected into the same site.

6.3 Shelf life

3 years
After reconstitution, immediate use is recommended.

6.4 Special precautions for storage

The vaccine should be stored in a refrigerator (2 °C – 8 °C). Do not freeze.

6.5 Nature and contents of container

Powder in a 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) – Box of 1

6.6 Instructions for use and handling

To reconstitute the vaccine:

- Take the cap off the vaccine vial
- Inject the content of the prefilled syringe into the vial of powder
- Shake gently to obtain a homogeneous suspension of the vaccine. The reconstituted vaccine appears as a clear liquid
- Immediately withdraw 0.5 ml of the suspension
- Inject

7 MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR
2 avenue du Pont Pasteur
69007 LYON

8 PRESENTATION AND ADMINISTRATIVE IDENTIFICATION NUMBER

336 604-9: Powder in a 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). Box of 1.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION