Public Assessment Report

VERORAB

INFORMASI PRODUK

Nama obat	:	Verorab
Bentuk sediaan	:	Serbuk Injeksi
Zat aktif	:	Tiap dosis 0,5 mL mengandung : Inactivated rabies virus (wistar pm/wi 38-1503-3m strain) NLT 2.5 iu
Kemasan	:	Dus, 1 vial @ 1 dosis + 1 syringe @ 0,5 ml NaCl 0.4 %
Pendaftar	:	PT. Aventis Pharma
Produsen	:	Sanofi Pasteur , Lyon, Perancis
Kategori Registrasi	:	Registrasi produk biologi yang sudah terdaftar dengan posologi baru

Sudah disetujui di Indonesia	Yang diajukan
<u>Posology</u> *The vaccination schedule should be adapted according to the circumstances of the vaccination and the subject's rabies immune status.* <u>Preventive or pre-exposure vaccination</u> *- Primary vaccination: 3 injections on D0, D7, D28, The injection scheduled on D28 may be administered on D21.* *- Booster injection 1 years later* *- Booster injections every 5 years* *The injection scheduled on D27 may be administered on D21.* *"Currative" vaccination (prevention of rabies after confirmed or suspected exposure)* *First aid treatment* *The treatment of wounds is very important and must be performed promptly after the bite. It is recommended firstly to wash the wound with large quantities of water and soap or detergent and then apply 70% alcohol, tincture of iodine or a 0.1 per cent quaternary ammonium solution (provided that no soap remains as these two products neutralize each*	<u>Posology</u> *Once the vaccine is reconstituted with 0.5 mL of solvent,* ***one intramuscular (IM) dose consists of 0.5 mL of reconstituted vaccine and one intradermal (ID) dose consists of 0.1 mL of reconstituted vaccine per injection site****.* <u>Pre-exposure prophylaxis</u> *For pre-exposure immunization, individuals can be vaccinated according to one of the vaccination schedules presented in Table 1 and according to official local recommendations when available:* **Table 1: Pre-exposure vaccination schedules** D0 / D7 / D21 or D28 Conventional regimen IM route - 0.5 mL: 1 dose / 1 dose / 1 dose One-week regimen [a] IM route - 0.5 mL: 1 dose / 1 dose / — Conventional regimen ID route - 0.1 mL: 1 dose / 1 dose / 1 dose One-week regimen [a] ID route - 0.1 mL: 2 doses [b] / 2 doses [b] / — a - This regimen should not be used for immunocompromised individuals b - One injection in each arm (for adults and children) or each anterolateral thigh (infants toddlers *Booster doses are determined based on the risk of exposure and on serological tests in accordance with official recommendations.* *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)).* <u>Post-exposure prophylaxis</u> *Post-exposure prophylaxis includes local nonspecific treatment of the wound, vaccination and, where appropriate, passive with rabies immunoglobulins.* *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*

other).
Currative vaccination must be administered under medical superv ision and only in a rabies treatment center.

immediately or as soon as possible after exposure. It must be performed before administration of vaccine or rabies immunoglobulins, when they are indicated. Post-exposure prophylaxis should be adjusted to the exposure category, the condition of the animal (see Table 3) and the vaccination status of the patient, in accordance with official recommendations (see Table 2, WHO recommendations).

Post-exposure prophylaxis should be performed as soon as possible after exposure under medical supervision and only at rabies treatment center.

If necessary, post-exposure prophylaxis can be supplemented by tetanus prophylaxis and antibiotic therapy to prevent the development of infections other than rabies.

Table 2: 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 animal not available for testing	Recommended post-exposure prophylaxis
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. 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 method 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 vaccine immediately and rabies immunoglobulin, 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 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 (see Table 3).
(b) This observation period applies 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 using appropriate laboratory methods (see Table 3).
(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.

Table 3: Course of action after exposure depending on the condition of the animal (WHO recommendations to be adapted according to local recommendations)

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.

<u>*Vaccination of non-immunised subjects*</u>
(subjects who did not receive preexposure vaccination)

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

<u>*Post-exposure prophylaxis of previously non-immunised subjects*</u>
Individuals not previously immunized can be vaccinated according to one of the vaccination schedules presented in Table 4:

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 administeredin the deltoid region at D7 and D21.*

Whatever the regimen used, rabies immunoglobulins should be administered at D0 concomitantly with the vaccine, in case of category III exposure (WHO classification).
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.*

If possible, the vaccine should be injected on the side opposite the immunoglobulin administration sites. In enzootic areas, the severity of certain exposures due to the severity of the lesions and/or location (proximity of the central nervous system), a late consultation or immune deficiency of the subject may justify, depending on the case, 2 injections on D0.

<u>Vaccination of subjects already immunized</u>
Vaccination administered less than 5 years previously (cell culture rabies vaccine): 2 injections: D0 D3.
Vaccination administered over 5 years previously or incomplete: 5 injections: D0, D3, D7, D14 and D28 with administration of immunoglobulins if required.
In practice, if the last booster dose was administered over 5 years previously or if the vaccinationis incomplete, the subject is considered to have an uncertain vaccination status.

Table 4: Post-exposure vaccination schedules in previously non-immunized subjects

	D0	D3	D7	D14	D21	D28
Essen regimen IM route - 0.5 mL	1 dose	1 dose	1 dose	1 dose		1 dose
Zagreb regimen IM route - 0.5 mL	2 doses[a]		1 dose		1 dose	
Updated Thai Red Cross regimen ID route - 0.1 mL	2 doses[b]	2 doses[b]	2 doses[b]			2 doses[b]
One week, four-site regimen ID route - 0.1 mL	4 doses[c]	4 doses[c]	4 doses[c]			

a. one injection in each of the two deltoids (for adults and children) or anterolateral thigh sites (infants and toddlers)
b. to be injected in 2 distinct sites, if possible contra-laterally.
c. to be injected in 4 distinct sites

Whatever the regimen used, vaccination must not be discontinued unless the contact animal is declared free from rabies after veterinary supervision (see Table 3).

Rabies immunoglobulins should be administered concomitantly with the vaccine, in case of category III exposure (WHO classification, see Table 2). If possible, the vaccine should be administered contralaterally to the immunoglobulin administration sites.

Refer to the Summary of Characteristics of the rabies immunoglobulins used.

In enzootic areas, the severity of certain exposures due to the severity of the lesions and/or location (proximity of the central nervous system), a late consultation or immune deficiency of the subject may justify, depending on the case, 2 injections on D0.

<u>Post-exposure prophylaxis of previously immunized subjects</u>
In accordance with official recommendations, this applies to subjects who have already received preexposure prophylaxis or postexposure prophylaxis or who discontinued post-exposure prophylaxis after receiving at least two doses of vaccine prepared in cell culture.

*These individuals should receive **one dose of vaccine intramuscularly (vaccine dose 0.5 mL) or intradermally (vaccine dose 0.1 mL) on each of days 0 and 3. Alternatively, 4 intradermal injections (vaccine dose 0.1 mL) can be given at 4 distinct sites at D0**.*

Rabies immunoglobulin is not indicated for previously immunized individuals.

<u>Immunocompromised subjects</u>
• Pre-exposure prophylaxis
For immunocompromised subjects, conventional 3-dose regimens should be used

	and serological test for neutralizing antibodies should be performed 2 to 4 weeks after vaccination to assess the need for an additional dose of vaccine. *• Post-exposure prophylaxis* *For immunocompromised subjects, a complete vaccination schedule should be administered post-exposure. Rabies immunoglobulins should be administered concomitantly with the vaccine in the event of any category II or III exposure.* *<u>Paediatric population</u>* *Children should receive the same doses as adults.*
Method of administration *To reconstitute vaccine, introduce the diluent into the vial of powder and shake thoroughly until the powder is completely suspended. The solution should be homogenous, clear and free of anyparticles. Withdraw the solution in a syringe.* *The vaccine must be injected immediately after reconstitution and the syringe must be destroyed after use.* *Do not inject via the intravascular route.* *The vaccine is administered by the intramuscular route only in the deltoid in adults and in the anterolateral region of the thigh muscle in children. Do not inject in the gluteal region.*	***Method of administration*** *Precautions to be taken before handling or administering the medicinal product.* *The vaccine is administered via the intramuscular route, in the anterolateral region of the thigh muscle in infants and young children and in the deltoid muscle in older children and adults.* *It can also be administered by intradermal (ID) route preferably on upper arm or forearm.* *Do not inject in the buttocks region.* *Do not inject via the intravascular route.* *For instructions on reconstitution of the medicinal product before administration, see Special Precautions for Disposal and other Handling.*

PENGANTAR

Verorab merupakan sediaan vaksin rabies inaktivasi yang dibuat menggunakan vero cell (Purified Vero Rabies Vaccine/PVRV) dan diinaktivasi dengan beta-propiolactone. Verorab telah mendapatkan ijin edar di Indonesia dan disetujui sebagai vaksinasi *pre* dan *post-exposure* terhadap rabies. Saat ini pendaftar mengajukan perubahan indikasi dan posologi baru terkait penambahan regimen intradermal.

ASPEK MUTU

N/A

ASPEK KHASIAT DAN KEAMANAN

Studi Non Klinik

N/A

Studi Klinik

Diserahkan 6 studi klinik, yaitu:

- Studi 16 (Sabchareon, 1998)
- Studi 17 (RAB13 CSR, Jaiiaroensup, 1998)
- Studi 21 (RAB19 CSR, Lang, 1999; Vien, 2008, 5 years follow-up)
- Sudi 28 (RAC17 CSR)
- Studi 37 (RAB40 CSR)
- Studi VAJ00001

Dari data klinik tersebut di atas, 4 studi yang menggunakan posologi sesuai yang diajukan yaitu studi 16 (Sabchareon, 1998), studi 28 (RAC17 CSR), studi 37 (RAB40 CSR), studi VAJ00001.

Hasil evaluasi terhadap studi-studi di atas:

1. Penambahan posologi pada indikasi vaksinasi *pre-exposure*:
   - Untuk penambahan alternatif regimen dosis intramuscular (IM, 0,5 mL/dosis) 2 dosis (1 dosis pada D0 dan D7), hasil studi VAJ00001 menunjukkan penurunan respon imun pada bulan ke-6, dimana serokonversi 98,6% pada 14 hari setelah dosis terakhir vaksinasi primer menurun menjadi 58,6% pada bulan ke-6.
   - Untuk penambahan alternatif regimen intra-dermal (ID, 0,1 mL/dosis) regimen ID 4 dosis (2 dosis pada D0 dan D7), hasil studi VAJ00001 menunjukkan penurunan respon imun pada bulan ke-6, dimana serokonversi 97,2% pada 14 hari setelah dosis terakhir vaksinasi primer menurun menjadi 65,2% pada bulan ke-6.
   - Untuk penambahan alternatif regimen intra-dermal (ID, 0,1 mL/dosis) regimen ID 3 dosis (1 dosis pada D0, D7 dan D21/28), hasil studi 16 menunjukkan penurunan respon imun pada bulan ke-6, dimana serokonversi 98,9% pada 28 hari setelah dosis terakhir vaksinasi primer menurun menjadi 50,6% pada bulan ke-6 dan 52,6%.
   - Data keamanan vaksin Verorab pada vaksinasi pre-exposure regimen IM 2 dosis (1 dosis pada 0,7 hari) ID 4 dosis (2 dosis pada 0, 7 hari) dan regimen ID 3 dosis (1 dosis pada 0, 7, 28 hari) menunjukkan profil keamanan yang dapat ditoleransi.

2. Penambahan posologi pada indikasi vaksinasi post-exposure:
   - Penambahan alternatif regimen pada previously non-immunised subjects:
     - Untuk penambahan alternatif regimen intra-dermal (ID) 8 dosis (updated Thai Red Cross regimen), yaitu 2 dosis D0, D3, D7 dan D28:
       - Hasil studi 28 menunjukkan respon imun nAb rabies yang baik dengan angka serokonversi mencapai 100% sampai hari ke-90. Pada 6 bulan setelah vaksinasi (D180), serokonversi masih tinggi, yaitu 97,6% dan 95,8%.
       - Hasil studi 37 pada pasien WHO kategori III menunjukkan respon imun nAb rabies yang baik dengan angka serokonversi mencapai 98,8% pada hari ke-14, 79,8% pada tahun pertama dan sekitar 60% sampai tahun ke-5.
     - Tidak diserahkan studi pendukung untuk penambahan alternatif regimen ID 6 dosis (Institute Pasteur Cambodia regimen), yaitu 2 dosis ID pada D0, 2 dosis ID pada D3, 2 dosis ID pada D7.
     - Untuk penambahan alternatif regimen ID 12 dosis (One week, four-site regimen), yaitu 4 dosis ID pada D0, D3, dan D7, hasil studi 37 menunjukkan:
       - pada pasien dengan WHO kategori II, vaksin Verorab memberikan respon imun nAb rabies yang baik dengan angka serokonversi mencapai 100% pada hari ke-14 dan dapat dipertahankan serokonversi >90% sampai tahun ke-5.
       - pada pasien WHO kategori III, vaksin Verorab yang dikombinasi dengan serum imunoglobulin Favirab menunjukkan respon imun nAb rabies yang baik dengan angka serokonversi mencapai 99,4% pada hari ke-14 dan dapat dipertahankan serokonversi >80% sampai tahun ke-5.
   - Perubahan posologi pada previously immunised subjects:
     - Untuk regimen 2 dosis ID atau IM dengan interval 3 hari antar dosis, hasil studi VAJ00001 menunjukkan bahwa pada subjek yang telah diimunisasi primer, vaksinasi post-exposure simulasi dengan 2 dosis ID atau IM (1 dosis pada D0 dan D3), yang diberikan 1 tahun setelah vaksinasi primer, vaksin Verorab memberikan respon imun yang baik dengan serokonversi pada 7 hari dan 14 hari mencapai 100% (regimen IM) dan 98,6% (regimen ID).
     - Tidak diserahkan studi pendukung untuk regimen 4 injeksi ID pada D0.
   - Data keamanan vaksin Verorab pada vaksinasi *post-exposure*, *non-immunized* dan *immunized subjects,* menunjukkan profil keamanan yang dapat ditoleransi.

3. Penggunaan pada subjek dibawah 2 tahun:
   - Diserahkan studi untuk penggunaan post-exposure (studi 37) yang merekrut subjek kurang dari atau sama dengan 50 tahun dengan 17 (2,8%) subjek diataranya berusia kurang dari 2 tahun. Hasil studi secara keseluruhan menunjukkan serokonversi yang baik (98,8-100%).
   - Tidak diserahkan studi pendukung untuk indikasi profilaksis *pre-exposure*.
   - Tidak diserahkan studi pendukung untuk posologi pada *immunocompromized subjects (pre-exposure* dan *post-exposure prophylaxis*)

KEPUTUSAN

Mempertimbangkan data khasiat dan keamanan tersebut di atas, diputuskan registrasi penambahan indikasi baru Verorab serbuk injeksi dapat **diterima dengan perbaikan indikasi dan posologi** sebagai berikut:

Posologi

Once the vaccine is reconstituted with 0.5 mL of solvent, one intramuscular (IM) dose consists of 0.5 mL of reconstituted vaccine and one intradermal (ID) dose consists of 0.1 mL of reconstituted vaccine per injection site.

Pre-exposure prophylaxis

For pre-exposure immunization, individuals can be vaccinated according to one of the vaccination schedules presented in Table 1 and according to official local recommendations when available:

Table 1: Pre-exposure vaccination schedules

	D0	D7	D21 or D28
Conventional regimen IM route - 0.5 mL	1 dose	1 dose	1 dose

Post-exposure prophylaxis

Post-exposure prophylaxis includes local non-specific treatment of the wound, vaccination and, where appropriate, passive with rabies immunoglobulins.

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. Postexposure prophylaxis should be adjusted to the exposure category, the condition of the animal (see Table 3) and the vaccination status of the patient, in accordance with official recommendations (see Table 2, WHO recommendations).

Post-exposure prophylaxis should be performed as soon as possible after exposure under medical supervision and only at rabies treatment center.

If necessary, post-exposure prophylaxis can be supplemented by tetanus prophylaxis and antibiotic therapy to prevent the development of infections other than rabies.

Table 2. WHO Guide for post exposure prophylaxis depending on severity of exposure (to be adapted according to local official recommendations).

(...)

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 (see Table 3).*
b. *This observation period applies 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 euthanized and their tissues examined using appropriate laboratory methods (see Table 3).*
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.*

Table 3. Course of action after exposure depending on the condition of the animal (WHO recommendations to be adopted according to local recommendations.

(...)
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*

Table 4: Post exposure vaccination schedules in previously non-immunized subjects

	D0	D3	D7	D14	D21	D28
Essen	1	1	1	1		1
regimen IM route - 0.5 mL	dose	dose	dose	dose		dose
Zagreb regimen IM route - 0.5 mL	2 doses[a]		1 dose		1 dose	

Immunogenicity and safety data in children < 2 years old are limited (see section on clinical studies).

Whatever the regimen used, vaccination must not be discontinued unless the contact animal is declared free from rabies after veterinary supervision (see Table 3).

Rabies immunoglobulins should be administered concomitantly with the vaccine, in case of category III exposure (WHO classification, see Table 2). If possible, the vaccine should be administered contralaterally to the immunoglobulin administration sites.

Refer to the Summary of Characteristics of the rabies immunoglobulins used.

In enzootic areas, the severity of certain exposures due to the severity of the lesions and/or location (proximity of the central nervous system), a late consultation or immune deficiency of the subject may justify, depending on the case, 2 injections on D0.

Post-exposure prophylaxis of previously immunized subjects

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

These individuals should receive one dose of vaccine intramuscularly (vaccine dose 0.5 mL) or intradermally (vaccine dose 0.1 mL) on each of days 0 and 3. Rabies immunoglobulin is not indicated for previously immunized individuals.

Pediatric population

Children should receive the same doses as adults.