This package insert is continually updated: please read carefully before using a new pack!

NOVARTIS VACCINES

For the use only of registered medical practitioners or a hospital or a laboratory

Package leaflet

Rabipur®

PCEC Rabies vaccine
(PCEC = Purified Chick Embryo Cell)
Active substance: Inactivated rabies virus

Composition

One vial of powder and solvent for solution for injection

After reconstitution, 1.0 ml contains:

Inactivated rabies virus (strain flury LEP), potency ≥ 2.5 IU.

Host system: Purified Chick Embryo Cells

Other ingredients :

Powder (Vials):

TRIS-(hydroxymethyl-)aminomethane, sodium chloride, EDTA (Titriplex III), potassium-L-glutamate, polygeline, saccharose,

Ampoule:

water for injections

Indications

Active immunisation against rabies in individuals of all ages.

a)Pre-exposure immunisation (preventative, prior to possible risk of exposure to rabies), in both primary series and booster dose: Immunisation prior to possible infection with rabies, particularly for anyone who is at continual, frequent or increased risk for exposure to the rabies virus, as a result of their residence or occupation, such as vets, veterinary medicine students, animal keepers, hunters, forestry workers, animal handlers, butchers, personnel in rabies research laboratories etc., or prior to visits to areas in which rabies is endemic (rabies infected areas). Children living in or visiting rabies-affected areas are at particular risk.

b) Post-exposure treatment (after suspected or proven exposure to rabies): The indication for post-exposure treatment with the rabies vaccine depends on the type of contact with the suspected rabid animal, as provided in Table, *Recommended post-exposure prophylaxis according to type of exposure.*

For further details, see enclosed tables.

Contraindications

Pre-exposure prophylaxis (PrEP)

Hypersensitivity

History of a severe hypersensitivity to the vaccine or any of the vaccine components constitutes a contraindication to pre-exposure vaccination with this vaccine.

Individuals with acute diseases requiring treatment should not be vaccinated until at least 2 weeks after recovery. Minor infections are not a contraindication to vaccination.

Post-exposure prophylaxis (PEP)

In view of the almost invariably fatal outcome of rabies, there is no contraindication to post-exposure prophylaxis, including pregnancy (1).

Hypersensitivity

Patients considered to be at risk of a severe hypersensitivity reaction to the vaccine or any of the vaccine components should be receive an alternative rabies vaccine if a suitable product is available.

Pregnancy and breast-feeding

No cases of harm attributable to use of this vaccine during pregnancy have been observed.

Rabipur may be administered to pregnant women when post-exposure prophylaxis is required.

The vaccine may also be used for pre-exposure prophylaxis during pregnancy if it is considered that the potential benefit outweighs any possible risk to the fetus.

While it is not known whether Rabipur enters breast milk, no risk to the breast-feeding infant has been identified. Rabipur may be administered to breastfeeding women when post-exposure prophylaxis is required.

The vaccine may also be used for pre-exposure prophylaxis in breastfeeding women if it is considered that the potential benefit outweighs any possible risk to the infant.

Special precautions for use

Reports of anaphylactic reactions including anaphylactic shock have occurred following Raipur vaccination., appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Rabipur contains residues of egg and chicken proteins, such as ovalbumin..

In instances in which individuals have reacted with clinical symptoms of anaphylaxis such as urticaria (nettle rash), upper airway (lip tongue, throat, laryngeal or epiglotal) oedema (inflammatory swelling of the lips and larynx region), laryngo- or bronchospasm (spasm of the glottis or bronchial muscles), a fall in blood pressure, or shock following exposure to egg or chicken protein, the immunisation should be conducted only under close clinical monitoring, and with the appropriate facilities for emergency treatment available.

Rabipur contains polygeline and may contain residual amounts of the antibiotics amphotericin B, chlortetracycline, neomycin and this could potentially cause allergic reactions.

Encephalitis and Guillain-Barre Syndrome have been reported to be temporally associated with the use of Rabipur. See section, *Undesirable effects*. The use of corticosteroids to treat adverse reactions such as these may inhibit the development of immunity to rabies. See *Interactions* section. A patient's risk of developing rabies must be carefully considered, before deciding to discontinue immunisation.

Do not administer by intravascular injection

If the vaccine is inadvertently administered intravascularly (in a blood vessel), there is a risk of adverse reactions, with shock potentially occurring in extreme cases. Appropriate emergency measures to prevent shock must be taken immediately.

People taking chloroquine for malaria treatment or prophylaxis may have a reduced response to intradermal rabies vaccination and should receive the vaccine intramuscularly (see section, *Interaction*).

Rabies vaccine must not be given by intra-gluteal injection or subcutaneously, as the induction of an adequate immune response may be less reliable.

Do not mix vaccine with rabies immunoglobulin in the same syringe (see section, *Interactions*).

Driving and using machines

No studies have been carried out with Rabipur to assess the effect on the ability to drive or use machines (see also section *Undesirable effects*).

Some of the adverse effects described in section *Undesirable effects* may affect the ability to drive and use machines.

Interactions

Immunocompromising conditions and immunosuppressive agents can interfere with the development of an adequate response to the rabies vaccine. Therefore, it is recommended that serological responses should be monitored in such subjects, and additional doses administered as necessary.

All of the rabies immunoglobulin, or as much as anatomically possible (but avoiding possible compartment syndrome), should be administered into or around the wound site or sites. The remaining immunoglobulin, if any, should be injected intramuscularly at a site distant from the site of vaccine administration to avoid possible interference with simultaneously administered rabies vaccine period. Concomitant vaccines should always be administrated at separate injection sites and preferably contralateral limbs.

The ID route must not be used in the following instances:

· Individuals receiving long term corticosteroid or other immunosuppressive therapy or chloroquine

· Immunocompromised individuals

Dosage and administration

Dosage in adults and children

The recommended single intramuscular (IM) dose is 1.0 ml in individuals of all ages.

The recommended single intradermal (ID) dose is 0.1 ml in individual of all ages.

Pre-exposure prophylaxis (PrEP)

Primary immunisation: intramuscular (IM) administration

In previously unvaccinated individuals, an initial course of pre-exposure prophylaxis consists of three doses (each of 1.0 ml) administered IM on days 0, 7, and 21 (or 28).

Pre-exposure prophylaxis is recommended for anyone who is at continual, frequent or increased risk for exposure to the rabies virus, as a result of their residence or occupation, such as laboratory workers dealing with rabies virus and other lyssaviruses, veterinarians and animal handlers. Travellers in high-risk areas should be vaccinated after a risk assessment. Children living in or visiting rabies-affected areas are at particular risk and should be given pre-exposure prophylaxis on an individual basis or in mass campaigns when there are no economic, programmatic or logistical obstacles (WHO 2013 recommendations)

Primary immunisation: intradermal (ID) administration

In previously unvaccinated individuals, an initial course of pre-exposure prophylaxis consists of three doses (each of 0.1 ml) administered ID on days 0, 7, and 21 (or 28).

BOOSTER DOSES

The individual IM booster dose is 1.0 ml.

The individual ID booster dose is 0.1 ml.

Rabipur may be used for booster vaccination after prior immunisation with human diploid cell rabies vaccine (HDCV).

The need of intermittent serological testing for the presence of antibody ≥ 0.5 IU/ml and the administration of booster doses should be assessed in accordance with official recommendations.

A booster would be recommended only if rabies virus neutralizing antibody (RVNA) concentration falls to less than 0.5 IU/ml (assessed by rapid fluorescent focus inhibition test (RFFIT) or fluorescent antibody virus neutralisation test (FAVNT)).

International recommendations (WHO) are as follows:

According to WHO, periodic booster doses of rabies vaccine are not necessary for people living in or travelling to high-risk areas who have received a complete primary series of pre- or post-exposure prophylaxis with rabies vaccine. Periodic booster injections are recommended only for people whose occupation puts them at continual or frequent risk of exposure as an extra precaution in the absence of recognized exposure. If possible, antibody monitoring of personnel at risk is preferred to the administration of routine boosters. For people who are potentially at risk of laboratory exposure to high concentrations of live rabies virus, antibody testing should be done every 6 months. If the titre falls below 0.5 IU/ml of serum, one booster dose of vaccine should be given intramuscularly <or intradermally>. Those professionals who are not at continual risk of exposure through their activities, such as certain categories of veterinarians and animal health officers, should have serological monitoring every 2 years (WHO 2013)

Alternatively, booster doses may be given at official recommended intervals without prior serological testing according to the perceived risk. Experience shows that reinforcing doses are generally required every 2-5 years.

Post-exposure prophylaxis (PEP)

Post-exposure prophylaxis consists of:

- local treatment of the wound as soon as possible after exposure,
- a course of potent, effective rabies vaccine that meets WHO recommendations and
- administration of rabies immunoglobulin, if indicated .

The indication for post-exposure prophylaxis depends on the type of contact with the suspected rabid animal, as provided in Table, *Recommended post-exposure prophylaxis according to type of exposure.* Post-exposure immunisation should begin as soon as possible after exposure and should be accompanied by local measures to the site of inoculation so as to reduce the risk of infection.

According to WHO, prompt local treatment of all bite wounds and scratches is an important step in post-exposure prophylaxis. The recommended first-aid procedures include immediate, thorough flushing and washing of the wound with soap and water, detergent, povidone iodine or other substances with virucidal activity. If soap or a virucidal agent is not available, the wound should be thoroughly and extensively washed with water. People who live in areas endemic for rabies should be taught simple local wound treatment and warned not to use procedures that may further contaminate or enlarge the wound.

●A bleeding wound at any site indicates potentially severe exposure and must be infiltrated with either human or equine rabies immunoglobulin. Most severe bite wounds are best treated by daily dressing, followed by secondary suturing when necessary. If suturing after wound cleansing cannot be avoided, the wound should first be infiltrated with human or equine rabies immunoglobulin and suturing delayed for several hours to allow diffusion of the immunoglobulin through the tissues before minimal sutures are applied. Secondary sutures are less likely to become infected and present better cosmetic results if carried out under optimal conditions. An infected bite wound is no contraindication to injection of rabies immunoglobulin. Bites on the finger or toe tip, ear lobe or nasal area can be safely injected with rabies immunoglobulin, provided excessive pressure is not applied, as this can cause compression syndromes. Other treatments, such as administration of antibiotics and tetanus prophylaxis, should be applied as appropriate for potentially contaminated wounds (WHO 2013).

- Post-exposure prophylaxis of previously unvaccinated individuals: IM administration
- 5 dose Essen regimen (1-1-1-1-1): one 1.0 ml IM injection on each of days 0, 3, 7, 14 and 28
- 4 dose Zagreb regimen (2-1-1): two 1.0 ml IM injections on day 0 (one in each of the two deltoids or thigh sites) followed by one 1.0 ml IM injection on each of days 7 and 21.

Post-exposure prophylaxis of previously unvaccinated individuals: ID administration

Updated two side Thai Red Cross (TRC) regimen (2-2-2-0-2): two 0.1 ml ID injections at different anatomical sites (e.g., deltoid and thigh) each on days 0, 3, 7, and 28.

Post-exposure prophylaxis in previously vaccinated individuals: IM administration

In previously vaccinated individuals, post-exposure prophylaxis consists of two doses (each of 1.0 ml) administered IM on days 0, and 3. Rabies immunoglobulin is not indicated in such cases.

Post-exposure prophylaxis in previously vaccinated individuals: ID administration

In previously vaccinated individuals, post-exposure prophylaxis consists of two doses (each of 0.1 ml) administered ID on days 0, and 3. Rabies immunoglobulin is not indicated in such cases.

Paediatric patients

Paediatric individuals receive the same 1.0 ml IM dose as adults.

Geriatric patients

Geriatric individuals receive the same 1.0 ml IM dose as adults.

Immunocompromised individuals (with impaired defense system):

In immunocompromised individuals, a complete series of 5 doses according to the Essen (1-1-1-1-1 on days 0, 3, 7, 14 and 28.) regimen in combination with comprehensive wound management and local infiltration of rabies immunoglobulin is required for individuals with category II and III exposure. See Table: *Recommended post-exposure prophylaxis according to type of exposure (WHO 2013).*

Alternatively, two doses of vaccine may be given on day 0, that is, a single dose of 1.0 ml vaccine should be injected into the right deltoid and another single dose into the left deltoid muscle. In small children, one dose should be given into the anterolateral region of each thigh. This would result in a total of 6 doses (2-1-1-1-1 on days 0, 3, 7, 14 and 28)

When feasible, the rabies virus neutralising antibody response should be measured 2 to 4 weeks (preferably on day 14) following the start of vaccination to assess the possible need for an additional dose of the vaccine. Immunosuppressive agents should not be administered during post-exposure therapy unless essential for the treatment of other conditions.

Method of administration

The lyophilisate should be reconstituted immediately using the diluent supplied. Mix gently to avoid foaming. The reconstituted vaccine should be used immediately.

Intramuscular (IM) Regimen: For adults and children ≥ 2 years of age, the vaccine should be administered into the deltoid; for children < 2 years, the anterolateral area of the thigh is recommended. The vaccine must not be given by intravascular injection.

Intradermal (ID) Regimen: Intradermal administration is an acceptable alternative to the standard intramuscular route, in countries where ID administration is endorsed by national health authorities, leading to significant vaccine savings.

Undesirable effects

Adverse reactions from clinical trials

In clinical studies the most commonly reported solicited adverse reactions were injection site pain (30-85%, mainly pain due to injection) or injection site induration (15-35%). Most injection site reactions were not severe and resolved within 24 to 48 hours after injection.

Adverse reactions from clinical trials are listed according to System Organ Classes in MedDRA. Within each System Organ Class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse reaction: very common (≥ 1/10); common (≥ 1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

The standard class system of the organs	Frequency	Adverse reactions
Blood and lymphatic system disorders	Common	Lymphadenopathy
Immune system disorders	Rare	Hypersensitivity (see also sections, Contraindications, and Special precautions for use)
Metabolism and nutrition disorders	Common	Decreased appetite
Nervous system disorders	Very common	Headache, dizziness
	Rare	Paraesthesia
Gastrointestinal Disorder	Common	Nausea, vomiting, diarrhoea, abdominal pain/discomfort
Skin and subcutaneous tissue disorders	Very common	Rash
	Common	Urticaria
	Rare	Increased sweating
Musculoskeletal disorders, connective tissue and bone	Common	Myalgia, arthralgia
General disorders and administration site conditions	Very common	Injection site reactions, malaise, fatigue, asthenia, fever
	Rare	Chills
	Very rarely	Circulatory instability

Adverse reactions from post-marketing spontaneous reports

The following adverse reactions have been identified during post approval use of Rabipur. Because these reactions are reported voluntarily from a population of uncertain size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness, frequency of reporting, causal connection to Rabipur, or a combination of these factors:

Immune System Disorders: Anaphylaxis including anaphylactic shock (see also section, Special precautions for use).

Nervous System Disorders: Encephalitis, Guillain-Barre Syndrome (see also section, Special precautions for use), vertigo.

Once initiated, rabies prophylaxis should not be interrupted or discontinued because of local or mild systemic adverse reactions to rabies vaccine. Usually such reactions can be successfully managed with anti-inflammatory and antipyretic agents (see sections *Special precautions* for use and *Interations*).

Storage and shelf life

Keep out of the sight and reach of children.

Do not use Rabipur after the expiry date which is stated on the label and carton.

Store protected from light in a refrigerator at +2°C to +8°C. Do not freeze.

After reconstitution the vaccine is to be used immediately.

Presentation and contents by weight, volume or number of item

Package with:

1 vial (type I glass) of freeze-dried vaccine with stopper (chlorobutyl)

1 ml solvent for solution in an ampoule (type I glass) with or without injection syringe (polypropylene with polyethylene plunger) with or without reconstitution needle and with or without needle for IM injection.

Not all pack sizes may be marketed.

Substance or indication category

Vaccines

Table: Recommended post-exposure prophylaxis according to type of exposure (WHO, 2013)

Category of exposure	Type of exposure to a domestic or wilda) [a]animal suspected or confirmed to be rabid, or animal unavailable for testing	Recommended post-exposure prophylaxis
I	Touching or feeding animals Licks on intact skin, Contact of intact skin with secretions or excretions of a rabid animal or human case	None, if reliable case history is available.
II	Nibbling of uncovered skin Minor scratches or abrasions without bleeding	Administer vaccine immediately [b] Stop treatment if animal remains healthy throughout an observation period of 10 days [c] or is proven to be negative for rabies by a reliable laboratory using appropriate diagnostic techniques.
III	Single or multiple transdermal bites[d] or scratches, licks on broken skin. Contamination of mucous membrane with saliva (i.e. licks). , Exposure to bats[e].	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 first vaccine dose administration. Stop treatment if animal remains healthy throughout an observation period of 10 days or is proven to be negative for rabies by reliable laboratory using appropriate diagnostic techniques

a) Exposure to rodents, rabbits or hares does not routinely require rabies post-exposure prophylaxis.
b) If an apparently healthy dog or cat in or from a low-risk area is placed under observation, treatment may be delayed.
c) 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.
d) Bites especially on the head, neck, face, hands and genitals are category III exposures because of the rich innervation of these areas.
e) Post-exposure prophylaxis should be considered when contact between a human and a bat has occurred, unless the exposed person can rule out a bite or scratch or exposure of a mucous membrane.

Additional Information

This vaccine conforms to the World Health Organisation (WHO) requirements and contains no preservative.

The antibody concentration achieved by the immunisation falls gradually; booster doses are therefore required to maintain immunity.

All immunisations and all immunoglobulins administered should be entered by the doctor, with the name of the preparation (proprietary name) and Lot. No., in the international immunisation record.

Optimal immunity will only be conferred if the full immunisation schedule is completed.

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January 2015

Name and address of the manufacturer:

CHIRON BEHRING VACCINES PVT. LTD.

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