1. NAME OF THE MEDICINAL PRODUCT

Rabipur
Powder and solvent for solution for injection.
Rabies, inactivated, whole virus vaccine.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 vial (1.0 ml) contains:
Rabies virus* (Inactivated, strain Flury LEP)…… ≥ 2.5 IU
* produced on purified chick embryo cells (PCEC)

This vaccine contains residues of polygeline, chicken proteins (e.g., ovalbumin), human serum albumin, and may contain traces of neomycin, chlortetracycline and amphotericin B. See sections 4.3 and 4.4.

For excipients see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Rabipur is a white, freeze-dried vaccine for reconstitution with the solvent prior to use.
The solvent is clear and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rabipur is indicated for active immunisation against rabies in individuals of all ages.

This includes pre-exposure prophylaxis (i.e. before possible risk of exposure to rabies), in both primary series and booster dose, and post-exposure prophylaxis (i.e. after suspected or proven exposure to rabies).

Rabipur is to be used on the basis of official recommendations.

4.2 Posology and method of administration

Posology

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 individuals 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.

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]).

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 RVNA concentration 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.

Booster: intradermal (ID) administration

The individual ID booster dose is 0.1 ml.

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 1, *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).

Table 1: Recommended post-exposure prophylaxis according to type of exposure (WHO 2013)

Category of exposure	**Type of exposure to a domestic or wild [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.

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.

Postexposure prophylaxis in unvaccinated individuals: ID administration

Updated two site 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.

Postexposure 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 or 0.1 ml ID dose as adults.

Geriatric patients
Geriatric individuals receive the same 1.0 ml IM dose or 0.1 ml ID dose as adults.

Immunocompromised individuals
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.

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 postexposure therapy unless essential for the treatment of other conditions (see section 4.5).

Method of administration
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.

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.

The vaccine must not be given by intravascular injection, see section 4.4.

Rabies vaccine must not be given by intra-gluteal injection or subcutaneously, see section 4.4.

For instructions on reconstitution of the vaccine before administration, see section 6.6.

4.3 Contraindications

Pre-exposure prophylaxis (PrEP)
History of a severe hypersensitivity to the active substance, any of the excipients listed in section 6.1 or residues in section 2

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.

4.4 Special warnings and precautions for use

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

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

Encephalitis and Guillain-Barré syndrome have been reported to be temporally associated with the use of Rabipur (see also section 4.8). The use of corticosteroids to treat adverse reactions such as these may inhibit the development of immunity to rabies (see section 4.5). A patient's risk of developing rabies must be carefully considered, before deciding to discontinue immunisation.

Unintentional intravascular injection may result in systemic reactions, including shock. Do not inject intravascularly. The vaccine must not be mixed in the same syringe with other medicinal products. If rabies immunoglobulin is indicated in addition to Rabipur vaccine, then it must be administered at an anatomical site distant to the vaccination (see section 4.5).

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions, may occur in association with vaccination as a psychogenic response to the needle injection (see section 4.8). It is important that procedures are in place to avoid injury from fainting.

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

4.5 Interaction with other medicinal products and other forms of interaction

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 (see section 4.2).

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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
No cases of harm attributable to use of Rabipur 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.

Breastfeeding
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.

Fertility
Non clinical reproductive and developmental toxicity studies have not been performed.

4.7 Effects on ability to drive and use machines

No studies have been carried out with Rabipur to assess the effect on the ability to drive or use machines (see also section 4.8).

Some of the adverse effects described in section 4.8, may affect the ability to drive and use machines.

4.8 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)

Blood and Lymphatic System Disorders

Common:	Lymphadenopathy

Immune System Disorders

Rare:	Hypersensitivity

Metabolism and Nutrition Disorders

Common:	Decreased appetite

Nervous System Disorders	
Very common:	Headache, dizziness
Rare:	Paraesthesia
Gastrointestinal Disorders	
Common:	Nausea, vomiting, diarrhoea, abdominal pain/discomfort
Skin and Subcutaneous Tissue Disorders	
Very common:	Rash
Common:	Urticaria
Rare:	Hyperhidrosis (sweating)
Musculoskeletal and Connective Tissue Disorders	
Common:	Myalgia, arthralgia
General Disorders and Administration Site Conditions	
Very common:	Injection site reactions, malaise, fatigue, asthenia, fever
Rare:	Chills

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 relationship to Rabipur, or a combination of these factors:

Immune System Disorders: Anaphylaxis including anaphylactic shock.

Nervous System Disorders: Encephalitis, Guillain-Barré syndrome, presyncope, syncope, vertigo

Skin and subcutaneous tissue disorders: Angioedema

Once initiated, rabies post-exposure prophylaxis should not be interrupted or discontinued because of local or mild systemic adverse reactions to rabies vaccine.

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 the national reporting system.

4.9 Overdose

No symptoms of overdose are known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: J07B G01

The minimum rabies virus antibody titre recommended as being proof of an adequate immune response after vaccination is ≥ 0.5 IU/ml concentration as specified by the WHO. In healthy vaccinees, this level should be achieved in most individuals by Day 14 of a postexposure regimen, with or without simultaneous administration of RIG and irrespective of age.

Pre-exposure prophylaxis

In clinical trials with previously unimmunised subjects, almost all subjects achieve an adequate immune response (RVNAs ≥ 0.5 IU/ml) 3 to 4 weeks after the end of a primary series of three injections of Rabipur when given according to the recommended schedule by the intramuscular and the intradermal route. Persistence of adequate immune response (RVNAs ≥ 0.5 IU/ml) for up to 2 years after immunization with Rabipur without additional booster has been found in clinical studies. As antibody concentrations slowly decrease, booster doses may be required to maintain antibody levels above 0.5 IU/ml. The need for and timing of boosting should be assessed on a case by case basis, taking into account official guidance (see also section 4.2).

In a clinical trial, a booster dose of Rabipur administered 1 year after primary immunisation elicited a 10-fold or higher increase in Geometric Mean Concentrations (GMCs) by day 30. It has also been demonstrated that individuals who had previously been immunised with Human Diploid Cell Vaccine (HDCV) developed a rapid anamnestic response when boosted with Rabipur.

Post-exposure prophylaxis

In clinical studies Rabipur elicited adequate neutralising antibodies (≥ 0.5 IU/ml) in almost all subjects by day 14 or 30, when administered according to the WHO- recommended 5- dose* (day 0, 3, 7, 14, 28; 1.0 ml each, intramuscular) Essen regimen or to the WHO recommended 4-dose (day 0 [2 doses], 7, 21; 1.0 ml each, intramuscular) Zagreb regimen, as well as the former WHO recommended 2-sites (day 0, 3, 7, 28; 0.1 ml per dose, 2 doses per each day, intradermal) TRC regimen..

* Former WHO recommended Essen regimen consisted of 6 doses (day 0, 3, 7, 14, 28, 90; 1.0 ml each, intramuscularly).

Concomitant administration of Human Rabies Immunoglobulin (HRIG) with the first dose of rabies vaccine caused a slight decrease in GMCs (Essen regimen). However, this was not considered to be clinically relevant nor statistically significant.

5.2 Pharmacokinetic properties

Not applicable

5.3 Preclinical safety data

Preclinical data including single-dose, repeated dose and local tolerance studies revealed no unexpected findings and no target organ toxicity. No genotoxicity, carcinogenicity and reproductive toxicity studies have been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Trometamol
Sodium chloride
Disodium edetate
Potassium-L-glutamate
Polygeline
Sucrose

Solvent:
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, Rabipur must not be mixed in the same syringe with other medicinal products.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Rabipur should be stored protected from light at 2°C to 8°C. Do not freeze.

After reconstitution the vaccine is to be used immediately.

The vaccine may not be used after the expiration date given on package and container.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

Instructions for Reconstituting Rabipur
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If either of these conditions exists, the vaccine should not be

administered. The vaccine should only be reconstituted using the solvent supplied in the package.

A clear colourless solution results after reconstitution of the white freeze-dried powder with the clear and colourless solvent.

The powder for solution should be reconstituted using the solvent for solution supplied and carefully agitated prior to injection. The reconstituted vaccine should be used immediately.

During manufacturing, the vial is sealed under vacuum. Therefore to prevent problems in withdrawing the reconstituted vaccine from the vial after reconstitution of the vaccine, it is recommended to unscrew the syringe from the needle to eliminate the negative pressure. After that, the vaccine can be easily withdrawn from the vial. It is not recommended to induce excess pressure, since over-pressurization will create the problems in withdrawing the proper amount of the vaccine.

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

7. NAME AND ADDRESS OF THE MANUFACTURER

CHIRON BEHRING VACCINES PVT. LTD.
501, Shree Amba Shanti Chambers,
Off Church Road, Andheri-Kurla Road,
Andheri (E)
Mumbai-400059
INDIA

8. DATE OF REVISION OF THE TEXT

06/2015