1. NAME OF THE MEDICINAL PRODUCT

Rabipur
Potency ≥ 2.5 IU/ml
Powder and solvent for solution for injection
Rabies, inactivated, whole virus vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (1 ml) contains:

Rabies virus* (Inactivated, strain Flury LEP)……≥ 2.5 IU
*produced on purified chick embryo cells (PCEC)

The 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 Contraindications and 4.4 Special warnings and special precautions for use.

For excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

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

The reconstituted product is clear to slightly opalescent and colourless to slightly pink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rabipur is indicated for active immunization 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).

4.2 Posology and method of administration

Posology
Dosage in adults and children
The recommended single intramuscular (IM) dose is 1.0ml in individuals of all ages.

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

Booster doses
The individual IM booster dose is 1ml.

Rabipur may be used for booster vaccination after prior immunization 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.

The following provides general guidance:

- Testing for neutralising antibodies at 6 month intervals is usually recommended if the risk of exposure is high (e.g. Laboratory staff working with rabies vaccine)
- In persons who are considered to be at continuing risk of exposure to rabies (e.g. veterinarians and their assistants, wildlife workers, hunters), a serological test should usually be performed at least every 2 years, with shorter intervals if appropriate to the perceived degree of risk.

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).

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 TREATMENT

Post-exposure prophylaxis consists of

- local treatment of the wound as soon as possible after exposure,
- a course of rabies vaccine that meets WHO recommendations
- 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.

Official guidance according to WHO PEP prophylaxis guideline should be sought regarding the appropriate concomitment measures that should be taken to prevent establishment of infection (see also section 4.4).

Table: 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:

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

Post-exposure prophylaxis in previously vaccinated individuals:
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.

Dosing in different populations:
Paediatric patients
Paediatric individuals receive the same 1.0ml IM dose as adults.

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

Immunocompromised patients
In immunocompromised patients, a complete series of 5 doses according to the (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).

Severely immunosuppressed patients may not develop an immunologic response after rabies vaccination.

In immunocompromised patients, the neutralising antibody titre should be measured 14 days after the first injection. Patients with a titre that is less than 0.5 IU/ml should be given another two doses of vaccine simultaneously and as soon as possible. Further checks on the antibody titre should be made and further doses of vaccine should be administered as necessary. Immunosuppressive agents should not be administered during post-exposure therapy unless essential for the treatment of other conditions.

In all cases, the immunisation schedule must be followed exactly as recommended, even if the patient does not present for treatment until a considerable time has elapsed since exposure.

Method of Administration
For adults and children ≥2 years of age, the vaccine should be given by intramuscular injection into the deltoid muscle; for children <2 years, the anterolateral region of the thigh is recommended.

The vaccine must not be given by intravascular injection (see Section 4.4 Special warnings and special precautions for use).

The vaccine does not contain a preservative. Therefore, great care must be taken to avoid contamination of the reconstituted vaccine.

The reconstituted product is clear to slightly opalescent and colourless to slightly pink.

4.3 Contraindications

History of a severe hypersensitivity to the vaccine or to any of the ingredients in the vaccine components constitutes a contraindication to pre-exposure vaccination with this vaccine (see sections 2 Qualitative and quantitative compositon and 6.1 List of excipients).
Individual with acute diseases requiring treatment should not be vaccinated until at least 2 weeks after recovery. Minor infections are not a contraindication to vaccination.

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 (see also section 4.4 Special warnings and special precautions for use, regarding previous hypersensitivity reactions).

In view of the almost invariably fatal outcome of rabies, no contraindication post-exposure treatment is indicated, including pregnancy.

4.4 Special warnings and special precautions for use

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

Rabipur contains residues of egg and chicken proteins, such as ovalbumin. In instances in which individuals have developed clinical symptoms of anaphylaxis such as generalized urticaria, upper airway (lip, tongue, throat, laryngeal or epiglottal) oedema, laryngeal or bronchospasm, hypotension or shock, following exposure to egg or chicken protein, the vaccination should only be administered by personnel with the capability and facilities to manage anaphylaxis post-vaccination.

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

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

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 Undesirable effects). It is important that procedures are in place to avoid injury from fainting.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

4.5 Interaction with other medicinal products and other forms of interaction

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 given as necessary.

Administration of rabies immunoglobulin may be necessary for management but may attenuate the effects of concomitantly administered rabies vaccine. Therefore, it is important that rabies immunoglobulin should be administered once only for treating each at-risk exposure and with adherence to the recommended dose.

All of the rabies immunoglobulin, or as much as anatomically possible (but avoiding possible compartment syndrome), should be administered into or around the wound sites. The remaining immunoglobulin, if any, should be injected intramuscularly at a site distant from the site of the vaccine administration to avoid possible interference with simultaneously administered rabies vaccine.

Other essential inactivated vaccines may be given at the same time as Rabipur.

Concomitant vaccines should always be administered at separate injection sites and preferably contralateral limbs.

4.6 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 pregnant and breastfeeding women when post-exposure treatment 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 development 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 section 4.8 Undesirable effects).

Some of the adverse effects described in section 4.8 Undesirable effects, 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 marked 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 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

Statistically there is no indication of increasing frequencies of primary manifestations or triggered attacks of autoimmune diseases (e.g. multiple sclerosis) after vaccination. However, in individual cases it cannot be absolutely excluded that a vaccination may trigger an episode in patients with corresponding genetic disposition. According to the current state of scientific knowledge vaccinations are not the cause of autoimmune disease.

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

Nervous System Disorders: Encephalitis, Guillain-Barre Syndrome (see also section 4.4 Special Warnings and Special precautions for use), presyncope, syncope, vertigo.

Skin and subcutaneous tissue disorders: Angioedema.

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. Please see section 4.4 Special warnings and special precautions for use and 4.5 Interaction with other medicinal products and other forms of interaction.

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 a 1:5 titre (complete inhibition in the rapid fluorescent focus inhibition [RFFIT] at 1:5 dilution) as specified by the CDC, or >0.5 IU/ml concentrations as specified by the WHO. In healthy vaccines, this level should be achieved in most individuals by Day 14 of a post-exposure 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) by day 28 of a primary series of three injections of Rabipur when given according to the recommended schedule by the intramuscular route.

As antibody titres slowly decrease, booster doses are required to maintain antibody levels above 0.5 IU/ml. However, persistence of adequate antibody concentrations for up to 2 years after immunisation with Rabipur without additional booster has been found to be 100 % in clinical trials.

Nevertheless, the need for and timing of boosting should be assessed on a case by case basis, taking into account official guidance (see also section on dosage).

In clinical trials, a booster dose of Rabipur 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 Treatment
In clinical studies, Rabipur elicited adequate neutralising antibodies (≥ 0.5 IU/ml) in almost all subjects by day14 or 30, when administered according to the WHO-recommended 5-dose* (day 0, 3, 7, 14 and 28; 1.0ml each, intramuscular) regimen, to the WHO recommended 4-dose (day 0 (2 doses), 7, 21; 1.0ml each, intramuscular) regimen.

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

Concomitant administration of either Human Rabies Immunoglobulin (HRIG) with the first dose of rabies vaccine caused a slight decrease in GMCs. 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 and reproductive toxicity studies have been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
TRIS-(hydroxymethyl)-aminomethane
Sodium chloride
Disodium edetate (Titriplex III)
Potassium-L-glutamate
Polygeline
Sucrose

Solvent (ampoule, syringe):
Water for injections

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

Store at +2° to +8° C (in a refrigerator). 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.

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 disposable syringe (polypropylene with natural rubber plunger stopper)

or

1 disposable pre-filled syringe (type 1 glass) of sterile diluents for reconstitution (1mL) with plunger-stopper (bromobutyl) without needle and with a tip-cap (bromobutyl).

1 small orange needle for injection (25 gauge, 1 inch) and one long green needle for reconstitution (21 guage, 1½ inch)

Not all pack sizes may be marketed.

6.5 Instructions for use and handling

Instructions for reconstituting Rabipur in ampoule

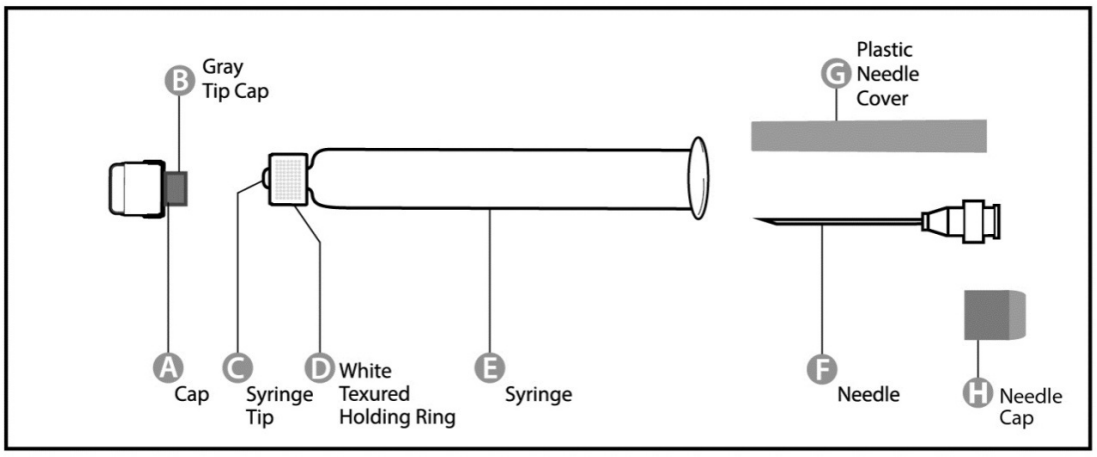
Parental drug products should be visually inspected for particulate matter and discoloration prior to administration. It must not be used if any change in the appearance of the vaccine has taken place. The vaccine should only be reconstituted using the solvent supplied in the package.

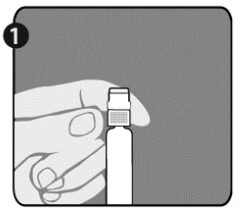
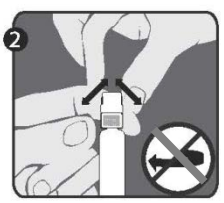
The reconstituted vaccine is clear to slightly opalescent and colourless to slightly pink.

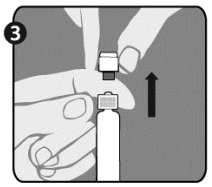
Mix gently to avoid foaming. The reconstituted vaccine should be used immediately.

The vial of the vaccine contains negative pressure. 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 problems in withdrawing the proper amount of vaccine.

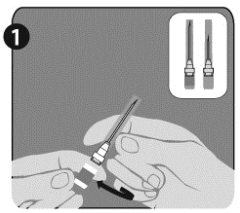
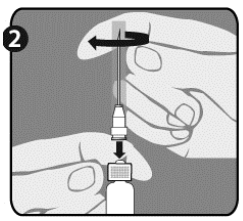
Instructions for use of Rabipur disposable pre-filled syringe
Pre-filled syringe



Step 1: With one hand, hold the syringe (E) with the cap pointing upward. Be sure to hold the syringe by the white textured holding ring (D).	
Step 2: With the other hand, grasp the cap (A) and firmly rock it back and forth to break its connection to the white textured holding ring (D). **Do not twist or turn the cap.**	

Step 3: Lift up to remove the cap (A) and the attached gray tip cap (B). Be careful not to touch the sterile syringe tip (C).	

Needle application (these instructions apply to both the green and the orange needles)

Step 1: Twist to remove the cap (H) from the green reconstitution needle. Do not remove the plastic cover (G). This needle is the longer of the two needles.	
Step 2: With one hand, firmly hold syringe (E) by white textured holding ring (D). With your other hand, insert needle (F) and twist clockwise until it locks into place. Once needle is locked, remove its plastic cover (G). The syringe (E) is now ready for use.	

Instructions for reconstituting Rabipur with the use of pre-filled syringe
The vaccine should be visually inspected both before and after reconstitution for any foreign particulate matter and or change in physical appearance. The vaccine must not be used if any change in the appearance of the vaccine has taken place.

The reconstituted vaccine is clear to slightly opalescent and colourless to slightly pink.

Mix gently to avoid foaming. The reconstituted vaccine should be used immediately.

The vial of vaccine contains negative pressure. 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 excessive pressure, since over-pressurization will create the problems in withdrawing the proper amount of the vaccine.

For presentations where needles are provided with the pre-filled syringe presentation
After completing the reconstitution of the vaccine, remove the cap from the orange administration needle (as explained in step 1 for the green needle) and replace the green reconstitution needle with the orange administration needle.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

GSK Vaccines GmbH
P.O. Box 1630
35006 Marburg
Germany

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF (PARTIAL) REVISION OF THE TEXT

03 July 2017 [GDS v5c (SI)]