1. NAME OF THE MEDICINAL PRODUCT

Rabipur ≥ 2.5 IU/ml, powder and solvent for solution for injection
Rabies vaccine for human use prepared in cell cultures

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

For excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

a) Pre-exposure prophylaxis (before possible risk of exposure to rabies)
b) Post-exposure treatment (after known or possible exposure to rabies)

Consideration should be given to national and/or WHO guidance regarding the prevention of rabies.

4.2 Posology and method of administration

Posology
The recommended single intramuscular dose is l ml in all age groups.

Whenever possible according to vaccine availabilility, it is recommended that one type of cell culture vaccine should be used throughout the course of pre- or post-exposure immunisation. However, adherence to the recommended schedules is of critical importance for post-exposure treatment, even if another type of cell culture vaccine has to be used.

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

Booster doses
The need of intermittent serological testing for the presence of antibody ≥ 0.5 IU/ml (as assessed by the Rapid Focus-Fluorescent inhibition Test) 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 virus).
- 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.
- In above mentioned cases, a booster dose should be given should the antibody titre fall below 0.5 IU/ml.
- 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.

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

POST-EXPOSURE TREATMENT

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 should be sought regarding the appropriate concomitant measures that should be taken to prevent establishment of infection (see also section 4.4).

Previously fully immunised individuals:

For WHO exposure categories II and III, and in category I cases where there is uncertainty regarding the correct classification of exposure (see Table l below), two doses (each of 1 ml) should be administered, one each on days 0 and 3. On a case by case basis, schedule A (see Table 2 below) may be applied if the last dose of vaccine was given more than two years previously.

Table 1: Immunisation schedules appropriate to different types of exposure (WHO 2002)

Exposure Category	**Type of contact with suspect or confirmed rabid domestic or wild animal, or animal unavailable for observation[a]**	**Recommended treatment**
I	Touching or feeding of animals Licks on intact skin Touching of inoculated animal lure with intact skin	None, if reliable case history is available. In case of unreliable case history, treat according to schedule A (see Table 2).
II	Nibbling of uncovered skin Minor scratches or abrasions without bleeding Licks on broken skin Touching of inoculated animal lure with skin damaged	Administer vaccine immediately [b] as in schedule A (see Table 2). In case of uncertainty and/or exposure in a high-risk area, administer active and passive treatment as in schedule B (see Table 2). (See also footnote [c])
III	Single or multiple transdermal bites or scratches Contamination of mucous membrane with saliva (i. e. licks) Touching of inoculated animal lure with mucous membrane or fresh skin wound	Administer rabies immunoglobulin and vaccine immediately [b] as in schedule B (see Table 2). (See also footnote [c])

[a] Exposure to rodents, rabbits and hares seldom, if ever, requires specific anti-rabies treatment.

[b] If an apparently healthy dog or cat in or from a low-risk area is placed under observation, it may be justified to delay specific treatment.

[c] Stop treatment if animal is a cat or dog and remains healthy throughout an observation period of 10 days or if animal is euthanised and found to be negative for rabies by appropriate laboratory techniques. Except in the case of threatened or endangered species, other domestic and wild animals suspected as rabid should be euthanised and their tissues examined using appropriate laboratory techniques.

Individuals unimmunised or with uncertain immune status

Depending on the WHO category as in Table l, treatment according to schedules A or B (see Table 2 below) may be required for previously unimmunised persons and for those who have received fewer than 3 doses of vaccine or who have received a vaccine of doubtful potency.

Table 2: Post-exposure treatment of subjects with no or uncertain immune status

Schedule A Active immunisation after exposure is required	Schedule B Active and passive immunisation after exposure are required
One injection of Rabipur i.m. on days: 0, 3, 7, 14, 28 (5-doses schedule) Or One dose of Rabipur is given into the right deltoid muscle and one dose into the left deltoid muscle on day 0, and one dose is applied into the deltoid muscle on days 7 and 21 (2-1-1 regimen). In small children the vaccine is to be given into the thighs.	Give Rabipur as in schedule A + l × 20 IU/kg body weight human rabies immunoglobulin* concomitantly with the first dose of Rabipur. If HRIG is not available at the time of the first vaccination it must be administered not later than 7 days after the first vaccination.

* Observe manufacturer's instructions regarding administration

Immunocompromised patients and patients with a particularly high risk of contracting rabies
For immunocompromised patients, those with multiple wounds and/or wounds on the head or other highly innervated areas, and those for whom there is a delay before initiation of treatment, it is recommended that:

- The days 0, 3, 7, 14 and 28 immunisation regimen should be used for these cases
- Two doses of vaccine may be given on day 0. That is, a single dose of 1 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.

Severely immunosuppressed patients may not develop an immunologic response after rabies vaccination. Therefore, prompt and appropriate wound care after an exposure is an essential step in preventing death. In addition, rabies immune globulin should be administered in all immunosuppressed patients experiencing Category II and Category III wounds.

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.

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
The vaccine should be given by intramuscular injection into the deltoid muscle, or into the anterolateral region of the thigh in small children.
It must not be given by intra-gluteal injection.
Do not administer by intravascular injection (see Section 4.4).

4.3 Contraindications

Post-exposure treatment
There are no contraindications to vaccination when post-exposure treatment is indicated. However, subjects considered to be at risk of a severe hypersensitivity reaction should receive an alternative rabies vaccine if a suitable product is available (see also section 4.4 regarding previous hypersensitivity reactions).

Pre-exposure prophylaxis
Rabipur should not be administered to subjects with a history of a severe hypersensitivity reaction to any of the ingredients in the vaccine. Note that the vaccine may contain polygeline , traces of neomycin, chlortetracycline, amphotericin B and chick proteins (see also section 4.4).
Vaccination should be delayed in subjects suffering from an acute febrile illness. Minor infections are not a contraindication to vaccination.

4.4 Special warnings and special precautions for use

As with all vaccines, appropriate medical treatment should be immediately available for use in the rare event of an anaphylactic reaction to the vaccine.
A history of allergy to eggs or a positive skin test to ovalbumin does not necessarily indicate that a subject will be allergic to Rabipur. However, subjects who have a history of a severe hypersensitivity reaction to eggs or egg products should not receive the vaccine for pre-exposure prophylaxis. Such subjects should not receive the vaccine for post-exposure treatment unless a suitable alternative vaccine is not available, in which case all injections should be administered with close monitoring and with facilities for emergency treatment.
Similarly, subjects with a history of a severe hypersensitivity reaction to any of the other ingredients in Rabipur such as polygeline (stabilizer), or to amphotericin B, chlortetracycline or neomycin (which may be present as trace residues) should not receive the vaccine for pre-exposure prophylaxis. The vaccine should not be given to such persons for post-exposure treatment unless a suitable alternative vaccine is not available, in which case precautions should be taken as above.

Do not administer by intravascular injection.
If the vaccine is inadvertently administered into a blood vessel there is a risk of severe adverse reactions, including shock

After contact with animals which are suspected carriers of rabies, it is essential to observe the following procedures (according to WHO 1997):

Immediate wound treatment
In order to remove rabies virus, immediately cleanse wound with soap and flush thoroughly with water. Then treat with alcohol (70%) or iodine solution. Where possible, bite injuries should not be closed with a suture, or only sutured to secure apposition.

Tetanus vaccination and rabies immunoglobulin administration
Prophylaxis against tetanus should be implemented when necessary.
In cases of indicated passive immunisation, as much of the recommended dose of human rabies immunoglobulin (HRIG) as anatomically feasible should be applied as deeply as possible in and around the wound. Any remaining HRIG should be injected intramuscularly at a site distant from the vaccination site, preferably intragluteally. For detailed information plesase refer to the SmPC and/or package insert of HRIG.

4.5 Interaction with other medicinal products and other forms of interaction

Patients who are immunocompromised, including those receiving immunosuppressive therapy, may not mount an adequate response to rabies vaccine. Therefore, it is recommended that serological responses should be monitored in such patients and additional doses given as necessary (see section 4.2 for details).
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.
Other essential inactivated vaccines may be given at the same time as Rabipur. Different injectable inactivated vaccines should be administered into separate injection sites.

4.6 Pregnancy and lactation

No cases of harm attributable to use of Rabipur during pregnancy have been observed. 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 during pregnancy and in breastfeeding women if it is considered that the potential benefit outweighs any possible risk to the fetus/infant.

4.7 Effects on ability to drive and use machines

The vaccine is unlikely to produce an effect on ability to drive and use machines.

4.8 Undesirable effects

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. Furthermore, the following undesirable effects were observed in clinical trials and/or during the post-marketing period:

Standard system organ class	**Frequency**	**Adverse reactions**
General disorders and administration site condition	Very common > 1/10	Injection site pain, injection site reaction, injection site induration
	Common > 1/100, < 1/10	Asthenia, malaise, fever, fatigue, influenza like illness, injection site erythema
Cardiac disorders	Rare > 1/10.000, < 1/1.000	Circulatory reactions (such as palpitations or hot flush)
Blood and lymphatic system disorders	Common > 1/100, < 1/10	Lymphadenopathy
Ear and labyrinth disorders	Very rare < 1/10.000	Vertigo
Eye disorders	Rare > 1/10.000, < 1/1.000	Visual disturbance
Nervous system disorders*	Common > 1/100, < 1/10	Headache

	Rare > 1/10.000, < 1/1.000	Paraesthesia
	Very rare < 1/10.000	Nervous system disorders (such as paresis or Guillain-Barré-Syndrome)
Skin disorders	Common > 1/100, < 1/10	Rash
Immune system disorders	Rare > 1/10.000, < 1/1.000	Allergic reactions (such as anaphylaxis, bronchospasm, oedema, urticaria or pruritus)
Musculosceletal and connective tissue disorders	Common > 1/100, < 1/10	Myalgia, arthralgia
Gastrointestinal disorders	Common > 1/100, < 1/10	Gastrointestinal disorder (such as nausea or abdominal pain)

* 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 diseases.

4.9 Overdose

No symptoms of overdose are known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC-Code: J07B G01

Pre-exposure Prophylaxis
In clinical trials with previously unimmunised subjects, almost all subjects achieve a protective antibody titre (≥ 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 protective antibody titres for 2 years after immunisation with Rabipur without additional booster has been found to be 100 % in clinical trials.
In clinical trials, a booster dose of Rabipur elicited a 10-fold or higher increase in Geometric Mean Titres (GMTs) 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.
Persistence of antibody titres has been shown for 14 years in a limited number (n = 28) of subjects tested.
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 4.2).

Post-exposure Treatment
In clinical studies, Rabipur elicited neutralising antibodies (≥ 0.5 IU/ml) in 98% of patients within 14 days and in 99-100% of patients by day 28 – 38, when administered according to the WHO-recommended schedule of five intramuscular injections of 1 ml, one each on days 0, 3, 7, 14 and 28.
Concomitant administration of either Human Rabies Immunoglobulin (HRIG) or Equine Rabies Immunoglobulin (ERIG) with the first dose of rabies vaccine caused a slight decrease in GMTs. However, this was not considered to be clinically relevant.

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:
Water for injections

6.2 Incompatibilities

This vaccine should not be mixed with other medicinal products.

6.3 Shelf life

4 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Pack containing
Powder in a vial (type I glass) 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)
Not all pack sizes may be marketed.

6.6 Instructions for use and handling

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. For appearance see Section 3.
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.
Any unused vaccine or waste material should be disposed of in accordance with local requirements.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

GSKVaccines GmbH
P.O. Box 1630
35006 Marburg
Germany

8. MARKETING AUTHORISATION NUMBER

PL 16033/0008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF (PARTIAL) REVISION OF THE TEXT

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