Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rabipur
Powder and solvent for solution for injection Rabies vaccine
(inactivated).

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 chicken proteins (e.g., ovalbumin), human serum albumin, and may contain traces of neomycin, chlortetracycline and amphotericin B. See section 4.4.

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection

The powder is white.
The solvent is clear and colourless.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

See Sections 4.2 and 5.1 for detailed information about pre- and post-exposure prophylaxis.

Rabipur should be used in accordance with official recommendations.

4.2 Posology and method of administration

Posology
The recommended dose for both primary immunization and boosters is 1.0 ml.

Pre-exposure prophylaxis

Primary immunization
In previously unvaccinated individuals three doses should be administered according to the conventional or rapid regimen as shown in Table 1.

Table 1 Primary immunization regimens

	Conventional regimen	*Rapid Regimen**
1st dose	Day 0	Day 0
2nd dose	Day 7	Day 3
3rd dose	Day 21 (or 28)	Day 7

*The rapid regimen should only be considered for adults aged 18-65 years not able to complete the conventional PrEP regimen within 21 or 28 days before protection is required.

Booster doses

Booster doses are generally recommended every 2-5 years. Timing for booster after vaccination with rapid regimen has not yet been established (see also section 5.1). Serological testing for the presence of antibody ≥ 0.5 IU/ml to assess the need for booster doses should be conducted in accordance with official recommendations.

Rabipur may be used to boost individuals previously immunized with any human diploid cell rabies vaccine.

Post-exposure prophylaxis

Post-exposure prophylaxis should commence as soon as possible after exposure.
Table 2 summarises recommendations for post-exposure prophylaxis including immunization, according to the type of exposure.

Table 2: Recommended post-exposure prophylaxis according to type of exposure

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.

In-post-exposure prophylaxis of previously unvaccinated individuals, the vaccine should be administered according to Table 3.

Table 3: Post-exposure immunization regimens for previously unvaccinated individuals

	Essen regimen (*5 doses*)	Zagreb regimen (*4 doses*)	Reduced Essen regimen (*4 doses*)[2]
1st dose	Day 0	Day 0, 2 doses[1]	Day 0
2nd dose	Day 3		Day 3
3rd dose	Day 7	Day 7	Day 7
4th dose	Day 14	Day 21	Day 14
5th dose	Day 28		

1one injection in each of the two deltoids or thigh sites

2 this shortened Essen regimen may be used as an alternative for healthy, fully immune competent, exposed people provided they receive wound care plus rabies immunoglobulin in category III as well as in category II exposures and a WHO-prequalified rabies vaccine

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

In immunocompromised individuals with category II and III exposures, 5 doses should be given in combination with comprehensive wound management and local infiltration of rabies immunoglobulin as shown in Table 4.

Table 4: Post-exposure immunization regimens for immunocompromised individuals

	Essen regimen	*Alternative to Essen*
1st dose	Day 0	Day 0, 2 doses[1]
2nd dose	Day 3	Day 3
3rd dose	Day 7	Day 7
4th dose	Day 14	Day 14
5th dose	Day 28	Day 28

1 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.

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).

Paediatric population

Paediatric individuals receive the same dose as adults (1.0 ml).

Method of administration

Rabipur is for intramuscular administration only. For adults and children ≥ 2 years of age, the vaccine should be

administered intramuscular into the deltoid muscle. For children < 2 years, the anterolateral area of the thigh is recommended.

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 reaction to the active substance, to any of the excipients listed in section 6.1 or to any of the residues listed in section 2.

Vaccination should be postponed in individuals with a severe febrile illness (see section 4.4).

Post-exposure prophylaxis (PEP)

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

4.4 Special warnings and precautions for use

A protective immune response may not be elicited in all vaccinees.

In case of acute diseases requiring treatment, patients should not be vaccinated until at least 2 weeks after recovery. The presence of a minor infection should not result in the deferral of vaccination.

Hypersensitivity reactions (PEP only)

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. Rabipur contains the excipient polygeline, residues of chicken proteins (e.g., ovalbumin), human serum albumin, and may contain traces of antibiotics (see section 2). 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 spasm or bronchospasm, hypotension or shock, following exposure to any of these substances, the vaccination should only be administered by personnel with the capability and facilities to manage anaphylaxis post-vaccination.

Central nervous system effects

Encephalitis and Guillain-Barré syndrome have been temporally associated with the use of Rabipur (see also section 4.8). A patient's risk of developing rabies must be carefully considered, before deciding to discontinue immunization.

Route of administration

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

Unintentional intravascular injection may result in systemic reactions, including shock. Do not inject intravascularly.

Anxiety-related reactions

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.

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).

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 an anatomical site distant to the vaccination.

Available clinical data support concomitant administration of Rabipur with inactivated Japanese encephalitis vaccine and conjugated MenACWY meningococcal vaccine in adult subjects; limited data are available in the paediatric population.

Almost all adult subjects achieved an adequate immune response (Rabies Viral Neutralizing Antibodies (RVNAs) ≥ 0.5 IU/ml) within 7 days after the end of a primary series of three injections of Rabipur when given concomitantly with inactivated JE vaccine according to either a rapid or the conventional PrEP schedule by the intramuscular route. From day 57 after vaccination a faster decline in immune response to rabies was observed in individuals vaccinated concomitantly with JE vaccine according to the rapid PrEP schedule compared with the concomitant conventional PrEP schedule and the rabies only conventional PrEP schedule. At day 366, percentages of subjects with RVNA concentration ≥0.5 IU/mL were 68%, 76%, and 80% for vaccine groups rabies/JE accelerated, rabies/JE conventional, and rabies conventional, respectively.

All adult subjects achieved an adequate immune response (RVNAs ≥ 0.5 IU/ml) within 28 days after the end of a primary series of three injections of Rabipur when given concomitantly with conjugated MenACWY vaccine according to the recommended conventional schedule by the intramuscular route.

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

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 foetus.

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

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

4.8 Undesirable effects

Summary of the safety profile

Anaphylactic reactions including anaphylactic shock that are very rare but clinically severe, and potentially lethal, systemic allergic reactions, can occur following Rabipur vaccination. Mild allergic reactions to Rabipur (i.e. hypersensitivity), including rashes (very common) and urticaria (common) may occur after vaccination. These reactions are usually mild in nature and typically resolve within a few days.

Very rare cases with symptoms of Encephalitis and Guillain-Barré Syndrome have been reported following Rabipur vaccination.

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

Tabulated list of adverse reactions

Adverse reactions considered as being at least possibly related to vaccination have been categorised by frequency.

Frequencies are defined as follows:

Very common: (≥1/10)

Common: (≥1/100 to <1/10)

Uncommon: (≥1/1,000 to <1/100)

Rare: (≥1/10,000 to <1/1,000)

Very rare: (<1/10,000)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

In addition to reports in clinical trials, worldwide voluntary reports of adverse reactions received for Rabipur since market introduction are included in the list. These reactions are reported voluntarily from a population of uncertain size and have been chosen for inclusion due to their seriousness, frequency of reporting, causal relationship to Rabipur, or a combination of these factors.

Table 5: Adverse reactions reported in clinical trials and in postmarketing surveillance

System Organ Class	**Frequency**	**Adverse events**
Blood and lymphatic system disorders	Common	Lymphadenopathy
Immune system disorders	Rare	Hypersensitivity
	Very rare	Anaphylaxis including anaphylactic shock*
Metabolism and nutrition disorder	Common	Decreased appetite
Nervous system disorders	Very common	Headache, Dizziness
	Rare	Paraesthesia
	Very rare	Encephalitis*, Guillain-Barré syndrome*, Presyncope*, Syncope*, Vertigo*
Gastrointestinal disorders	Common	Nausea, Vomiting, Diarrhoea, Abdominal pain/ discomfort
Skin and subcutaneous tissue disorders	Very common	Rash
	Common	Urticaria
	Rare	Hyperhidrosis (sweating)
	Very rare	Angioedema*
Musculoskeletal and connective tissue disorders	Common	Myalgia, Arthralgia
General disorder and administration site conditions	Very common	Injection site reactions, Malaise, Fatigue, Asthenia, Fever
	Rare	Chills

*Additional adverse reactions from spontaneous reporting

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

No symptoms of overdose are known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: J07B G01

Mechanism of action

Rabipur induces stimulation of lymphocytes and antibody-secreting plasmocytes resulting in production of RVNAs.

Clinical efficacy and safety

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 route.

Persistence of adequate immune response (RVNAs ≥ 0.5 IU/ml) for up to 2 years after primary immunization with Rabipur without booster doses 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 timing of booster after primary vaccination with rapid regimen or after concomitant vaccination has not yet been established. Due to a faster decline in immune response compared with the conventional schedule a shorter interval between primary vaccination and booster administration may be needed compared with the conventional vaccine schedule (see 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 5- dose (day 0, 3, 7, 14, 28; 1.0 ml each, intramuscular) Essen regimen or 4-dose (day 0 [2 doses], 7, 21; 1.0 ml each, intramuscular) Zagreb regimen.

Concomitant administration of Human Rabies Immunoglobulin with the first dose of rabies vaccine caused a slight decrease in GMCs (Essen regimen). 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, 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

After reconstitution the vaccine is to be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

Keep the vial and the ampoule in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3 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 ampoule (type I glass) of Sterile Diluent for reconstitution (1 mL) with or without injection syringe (polypropylene with polyethylene plunger)

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other 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.

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 MARKETING AUTHORISATION HOLDER

GSK Vaccines GmbH
Emil-von-Behring Strasse 76
35041 Marburg
Germany

8 MARKETING AUTHORISATION NUMBER

PA0877/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 2 April 2004
Date of last renewal: 3 March 2010

10 DATE OF REVISION OF THE TEXT

June 2018