PRODUCT MONOGRAPH

RABAVERT

Rabies Vaccine

Lyophilized powder for reconstitution with a diluent
2.5 IU of rabies antigen

Therapeutic Classification: Active Immunising Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients (per 1 mL)
Intramuscular (IM) Injection	Lyophilized powder for reconstitution with a diluent / ≥ 2.5 IUs of rabies antigen per 1 mL	Disodium edetate, hydrogen chloride, polygeline, potassium-L-glutamate, sodium chloride, sucrose, trometamol, water for injection. Residues*: Amphotericin B, chlortetracycline, human serum albumin, neomycin, and ovalbumin

*From the manufacturing process

DESCRIPTION

RABAVERT (Rabies Vaccine) is a sterile lyophilized powder obtained by growing the fixed-virus strain Flury LEP in primary cultures of chicken fibroblasts. The strain Flury LEP was obtained from American Type Culture Collection as the 59th egg passage. The growth medium for propagation of the virus is a synthetic cell culture medium with the addition of human albumin, polygeline (processed bovine gelatin) and antibiotics.

The virus is inactivated with β-propiolactone, and further processed by zonal centrifugation in a sucrose density-gradient. The vaccine is lyophilized after addition of a stabilizer solution which consists of buffered polygeline and potassium glutamate.

One dose of reconstituted vaccine contains ≤12 mg polygeline (processed bovine gelatin), ≤0.3 mg human serum albumin, 1 mg potassium-L-glutamate, and 0.3 mg disodium edetate. Small quantities of bovine serum are used in the cell culture process. Bovine components originate only from source countries known to be free of bovine spongiform encephalopathy. Minimal amounts of chicken protein may be present in the final product; ovalbumin content is ≤3 ng/dose (1 mL), based on ELISA. In the final vaccine, neomycin is present at ≤10 mcg, chlortetracycline at ≤200 ng, and amphotericin B at ≤20 ng per dose.

RABAVERT is intended for intramuscular (IM) injection. The vaccine contains no preservative and should be used immediately after reconstitution with the supplied Sterile Diluent for RABAVERT (Water for Injection).

The potency of the final product is determined by the US National Institute of Health (NIH) mouse potency test using the US reference standard. The potency of one dose (1.0 mL) RABAVERT is at least 2.5 IU of rabies antigen.

RABAVERT is a white, lyophilized powder for reconstitution with the water for injection diluent prior to use; the reconstituted vaccine is a clear to slightly opalescent, colorless to slightly pink solution.

INDICATIONS AND CLINICAL USE

RABAVERT (Rabies Vaccine) is indicated for:

- Pre-exposure vaccination, in both primary series and booster doses against rabies in all age groups.
- Post-exposure prophylaxis against rabies in all age groups.

Pre-Exposure Vaccination

Primary immunization

Pre-exposure rabies immunization is an elective procedure and should be offered to people at potential risk of contact with rabid animals, e.g., certain laboratory workers, veterinarians, animal control and wildlife workers, spelunkers, and hunters and trappers in high-risk areas such as the Far North. Travellers to endemic areas where there is not likely to be access to adequate and safe post-exposure measures should consider pre-travel immunization. As well, children who are too young to understand either the need to avoid animals or to report a traumatic contact are considered at greater risk of rabid animal exposure and should be offered pre-exposure immunization when travelling to endemic areas.

Booster doses

People with continuing high risk of exposure, such as certain veterinarians, should have their serum tested for rabies antibodies every 2 years by the Rapid Fluorescent-Focus Inhibition Test (RFFIT); others working with live rabies virus in laboratories or vaccine production facilities who are at risk of unapparent exposure should be tested every 6 months.

Those with inadequate titres should be given a booster dose of RABAVERT.

Alternatively, booster doses may be given every 2-5 years, if situation does not warrant continual serological control and depending on the level of exposure risk.

Post-Exposure Prophylaxis

Table 1 outlines the recommendations for the management of people after possible exposure to rabies. These recommendations are intended as a guide and may need to be modified in accordance with the specific circumstances of the exposure.

Immediate washing and flushing with soap and water and a virucidal agent is imperative. Suturing the wound should be avoided if possible. Tetanus prophylaxis and antibacterial drugs should be given as required.

Table 1 - Post-exposure prophylaxis for people not previously immunized against rabies

Animal species	Condition of animal at time of exposure	Management of exposed person
Dog or cat	Healthy, and available for 10 days observation	1. Local wound treatment 2. At first sign of rabies in animal, give RIG and start RABAVERT
	Rabid or suspected to be rabid* Unknown or escaped	1. Local wound treatment 2. RIG and RABAVERT
Skunk, bat, fox, coyote, raccoon and other carnivores. Included bat found in room when a person was sleeping unattended.	Regard as rabid unless geographic area is known to be rabies free*	1. Local wound treatment 2. RIG and RABAVERT
Livestock, rodents or lagomorphs (hares and rabbits)	Consider individually. Consult appropriate public health and Food Inspection Agency officials. Bites of squirrels, chipmunks, rats, mice, hamsters, gerbils, other rodents, rabbits and hares may warrant post-exposure rabies prophylaxis if the behavior of the biting animal was highly unusual.	

RIG = (human) rabies immunoglobulin

*If possible, the animal should be humanely killed and the brain tested for rabies as soon as possible; holding for observation is not recommended. Discontinue vaccination if fluorescent antibody test of animal brain is negative.

The following factors should be considered before antirabies treatment is initiated.

Species of Biting Animal

The animals in Canada most often proven rabid are wild terrestrial carnivores (raccoons, foxes, and skunks), wild dogs and cats, bats, and cattle. The distribution of animal rabies and the species involved vary considerably across Canada by region and over time, so in cases of possible exposure it is important to consult the local medical officer or government veterinarian. Human exposures to livestock are usually confined to salivary contamination with the exception of horses and swine, for which bites have been reported. Risk of infection after exposure to

rabid cattle is low. Squirrels, hamsters, guinea-pigs, gerbils, chipmunks, rats, mice, other rodents, rabbits and hares are only rarely found to be infected with rabies and are not known to have caused human rabies in North America; post-exposure prophylaxis should be considered only if the animal's behavior was highly unusual.

The manifestations of rabies and the incubation periods vary in different species. The length of time virus may be excreted in saliva before the development of symptoms has not been determined for the purpose of defining rabies exposure except in domestic dogs, cats and ferrets. In these animals, rabies virus excretion does not generally preceed symptom development beyond 10 days. It remains unclear as to whether asymptomatic carriage of rabies virus in animals in the wild is possible.

Circumstances of Biting Incident

An UNPROVOKED attack is more likely than a provoked attack to indicate the animal is rabid. Nevertheless, rabid cats and dogs may become uncharacteristically quiet. Bites inflicted on a person attempting to feed or handle an apparently healthy animal should generally be regarded as PROVOKED. A currently vaccinated dog, cat or ferret is unlikely to become infected with rabies.

Type of Exposure

Rabies is transmitted when the virus is inoculated into tissue. This occurs most commonly when rabies virus in saliva is introduced into tissues by bites. Transmission can also occur when cuts or wounds of skin or mucous membranes are contaminated with virus in saliva or infected tissues. Rarely, transmission has been recorded when virus was inhaled, or infected corneal grafts or solid organs were transplanted into patients. Thus, two broad categories of exposure are recognized as warranting post-exposure prophylaxis:

Bite: This is defined as any penetration of skin by teeth. Bites inflicted by most animals are readily apparent. However, bites inflicted by bats to a sleeping person may not be felt, and may leave no visible bite marks. Hence, when people are sleeping unattended in a room where a bat is or was present or when the possibility of a bite cannot be reasonably excluded (e.g., if a bat is discovered in proximity to an individual who is cognitively impaired) post-exposure prophylaxis should be initiated.

Non-bite: This category includes contamination of scratches, abrasions or cuts of skin or mucous membranes by saliva or other potentially infectious material, such as the brain tissue of a rabid animal. Petting a rabid animal or handling its blood, urine or feces is not considered to be an exposure nor is being sprayed by a skunk. These incidents do not warrant post-exposure prophylaxis.

Post-exposure prophylaxis is warranted and recommended in rare instances of non-bite exposure, such as inhalation of aerosolized virus by spelunkers exploring caves inhabited by infected bats or by laboratory technicians homogenizing tissues infected with rabies virus; however, the efficacy of prophylaxis after such exposures is unknown. Stringent guidelines concerning the

suitability of tissue donors have almost eliminated the possibility that rabies virus may be transmitted iatrogenically.

Exposures incurred in the course of caring for humans with rabies could theoretically transmit the infection. No case of rabies acquired in this way has been documented, but post-exposure prophylaxis should be considered for exposed individuals.

Because some bat bites may be less severe, and therefore more difficult to recognize, than bites by larger mammalian carnivores, rabies post-exposure prophylaxis should be considered for any physical contact with bats when bites or mucous membrane contacts cannot be excluded.

Vaccination Status of Biting Animal

A small number of vaccinated animals have developed rabies. Therefore, symptoms suggesting rabies, even in a vaccinated animal, must be carefully evaluated. The vaccination history in itself should not influence the need for post-exposure prophylaxis nor the need to sacrifice the animal for assessment.

Geriatrics (65 years and over):

Clinical studies of RABAVERT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Pediatrics (under 18 years):

The indication for children and infants is the same as for adults (see ACTION AND CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

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

As with other vaccines, pre-exposure vaccination with RABAVERT should be postponed in subjects suffering from an acute severe febrile illness. The presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

Hypersensitivity

History of anaphylaxis to the vaccine or any of the vaccine components, including the container, constitutes a contraindication to pre-exposure vaccination with this vaccine.

In the case of post-exposure prophylaxis, if an alternative product is not available, the patient should be vaccinated with caution with the necessary medical equipment and emergency supplies

available and observed carefully after vaccination. A patient's risk of acquiring rabies must be carefully considered before deciding to discontinue vaccination. Advice and assistance on the management of serious adverse reactions for persons receiving rabies vaccines may be sought from the appropriate health department.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Anaphylaxis, neuroparalytic events such as encephalitis, transient paralysis and Guillain-Barré Syndrome have been reported to be temporally associated with the use of RABAVERT (Rabies Vaccine). Also see below in WARNINGS AND PRECAUTIONS and in ADVERSE REACTIONS.

A patient's risk of developing rabies must be carefully considered, however, before deciding to discontinue immunization.

RABAVERT must not be used subcutaneously and should not be used intradermally.

Do not inject intravascularly.

General

Care is to be taken by the health-care provider for the safe and effective use of the product. The health-care provider should also question the patient, parent or guardian about:

1) the current health status of the vaccinee; and
2) reactions to a previous dose of RABAVERT, or a similar product.

Pre-exposure vaccination should be postponed in the case of sick and convalescent persons, and those considered to be in the incubation stage of an infectious disease.

A separate, sterile syringe and needle must be used for each patient to prevent transmission of hepatitis and other infectious agents from person to person. Needles must not be recapped and should be properly disposed of.

As with any rabies vaccine, vaccination with RABAVERT may not protect 100% of susceptible individuals.

RABAVERT must be injected intramuscularly. For adults, the **deltoid area** is the preferred site of immunization; for small children and infants, administration into the anterolateral zone of the thigh is preferred. The use of the gluteal region should be avoided, since administration in this area may result in lower neutralizing antibody titres (see DOSAGE AND ADMINISTRATION). The vaccine must not be mixed in the same syringe with other medicinal products. If rabies immunoglobulin is indicated in addition to RABAVERT vaccine, then it must be administered at

an anatomical site distant to the vaccination (see DRUG INTERACTIONS). Concomitant vaccines should always be administered at separate injection sites and preferably into different limbs.

Unintentional intravascular injection may result in systemic reactions, including shock. Immediate measures include catecholamines, volume replacement, high doses of corticosteroids, and oxygen.

Development of active immunity after vaccination may be impaired in immune-compromised individuals. Please refer to DRUG INTERACTIONS.

This product contains albumin, a derivative of human blood. It is present in RABAVERT at concentrations of ≤0.3 mg/dose. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of variant Creutzfeld-Jakob disease (vCJD) also is considered extremely remote. No cases of transmission of viral diseases or vCJD have ever been identified for albumin.

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

A history of allergy to eggs or a positive skin test to ovalbumin does not necessarily indicate that a subject will be allergic to RABAVERT. However, subjects who have a history of a severe hypersensitivity reaction to eggs or egg products should not receive the vaccine for pre-exposure vaccination. Such subjects should also not receive the vaccine for post-exposure prophylaxis 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 RABAVERT 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 vaccination. The vaccine should also not be given to such persons for post-exposure prophylaxis unless a suitable alternative vaccine is not available, in which case precautions should be taken as above.

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.

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 ADVERSE REACTIONS). It is important that procedures are in place to avoid injury from fainting.

Other events that have been reported in post-market surveillance as temporally associated with the use of RABAVERT include meningitis, myelitis, retrobulbar neuritis and multiple sclerosis. See ADVERSE REACTIONS. The use of corticosteroids to treat adverse reactions such as these and those listed in the Serious Warnings and Precautions above, may inhibit the development of immunity to rabies.

Carcinogenesis and Mutagenesis

Long-term studies with RABAVERT have not been conducted to assess the potential for carcinogenesis, mutagenesis, or impairment of fertility.

Special Populations

Pregnant Women: Animal reproductive studies have not been conducted with RABAVERT. It is also not known whether RABAVERT can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. No reports on adverse effects associated with the use of RABAVERT in pregnancy have been received.

Because of the potential consequences of inadequately treated rabies exposure, pregnancy is not considered a contraindication to post-exposure prophylaxis. If there is a substantial risk of exposure to rabies, pre-exposure vaccination may also be indicated during pregnancy.

Nursing Women: It is not known whether RABAVERT is excreted in animal or human milk.

Because of the potential consequences of inadequately treated rabies exposure, nursing is not considered a contraindication to post-exposure prophylaxis. If there is a substantial risk of exposure to rabies, pre-exposure vaccination may also be indicated during nursing.

Monitoring and Laboratory Tests

When rabies post-exposure prophylaxis is administered to persons receiving corticosteroids or other immunosuppressive therapy, or who are immunosuppressed, it is important that a serum sample on Day 14 (the day of the fourth vaccination) be tested for rabies antibody to ensure that an acceptable antibody response has been induced (RFFIT).

ADVERSE REACTIONS

As with all vaccines and as outlined below, RABAVERT (Rabies Vaccine) administration may cause unintended reactions. However, not all events occurring after vaccination are causally related to the vaccine. For any unexpected effects while taking RABAVERT, contact your physician or pharmacist.

Adverse Drug Reaction Overview

Adverse reactions reported are listed according to the following frequency:

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

In very rare cases, neurological and neuroparalytical events and rare cases of hypersensitivity reactions have been reported in temporal association with administration of RABAVERT.

The most commonly occurring adverse reactions are injection -site reactions, such as injection-site erythema, induration and pain; flu-like symptoms, such as asthenia, fatigue, fever, headache, myalgia and malaise; arthralgia, dizziness, lymphadenopathy, nausea, and rash.

A patient's risk of acquiring rabies must be carefully considered before deciding to discontinue vaccination. Advice and assistance on the management of serious adverse reactions for persons receiving rabies vaccines may be sought from the health department.

Clinical Trial Adverse Drug Reactions

As clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates.

The data from clinical trials described below (Table 2) reflect exposure to RABAVERT in 1,307 subjects, including 355 subjects in pre-exposure vaccination settings and 952 patients, who received RABAVERT for post-exposure prophylaxis. RABAVERT was studied primarily in single-blind, randomized controlled trials. The population studied was mainly Caucasian and Asian, ranging from healthy infants to healthy adults with an equal gender distribution. Patients only received IM administration of RABAVERT.

Table 2 – Adverse reactions information (clinical trials)

Body System	Frequency	Adverse Reactions (Clinical Trials, n=1,307)
General disorders and administration-site condition	Very common > 10%	Injection-site pain, injection-site reaction, injection-site induration, asthenia, malaise, fever, fatigue
	Common > 1%, < 10%	Influenza-like illness, injection-site erythema
	Rare ≥ 0.01%, < 0.1%	Chills
Blood and lymphatic system disorders	Common > 1%, < 10%	Lymphadenopathy
Nervous system disorders	Very Common > 10%	Dizziness, headache
	Rare ≥ 0.01%, < 0.1%	Paraesthesia
Skin and subcutaneous tissue disorders	Very Common > 10%	Rash
	Common > 1%, < 10%	Urticaria
	Rare ≥ 0.01%, < 0.1%	Hyperhidrosis (sweating)
Musculoskeletal and connective tissue disorders	Common > 1%, < 10%	Myalgia, arthralgia
Gastrointestinal disorders	Common > 1%, < 10%	Gastrointestinal disorders (such as nausea, vomiting, diarrhea or abdominal pain)
Metabolism and Nutrition Disorders	Common > 1%, < 10%	Decreased appetite
Immune System Disorders	Rare ≥ 0.01%, < 0.1%	Hypersensitivity

Post-Marketing Adverse Drug Reactions

Those adverse reactions identified during post-approval use of RABAVERT can be found in the following table (Table 3). As these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Decisions to include these reactions in labelling are typically based on one or more of the following factors: 1) seriousness of the reaction, 2) frequency of reporting, or 3) strength of causal connection to vaccine exposure, or a combination of these factors.

Table 3 - Adverse reactions information (post-marketing)

Body System	**Adverse Reactions (only observed in post-approval use, n ≥ 10,000,000); frequency < 1:1,000 for all events**
General disorders and administration-site condition	Chills, sweating
Cardiac disorders	Circulatory reactions (such as palpitations or hot flush)
Ear and labyrinth disorders	Vertigo
Eye disorders	Visual disturbance
Nervous system disorders	Paraesthesia
	Nervous system disorders (such as presyncope, syncope, encephalitis, transient paralysis or Guillain-Barré Syndrome)
Immune system disorders	Allergic reactions (such as anaphylaxis including anaphylactic shock, bronchospasm, oedema, or pruritus)
	Type III hypersensitivity-like symptoms
Skin and Subcutaneous Tissue Disorders	Angiodema, urticaria (common)
Musculoskeletal and connective tissue disorders	Pain in limbs, limb swelling

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 WARNINGS AND PRECAUTIONS section).

In addition to the reactions outlined above, the following adverse events have been reported very rarely following widespread use of the vaccine. A causal relationship to the vaccine has not been established for any of these events: aphasia, cardiovascular disorder, conversion disorder, convulsion, diabetes mellitus, eye disorder, hearing impairment, meningitis, multiple sclerosis, nephritis, pneumonia, polymyalgia rheumatica, respiratory disorder, somnolence, spontaneous abortion, thrombocytopenia.

Adherence to treatment guidelines, as outlined below, are of utmost importance in order to minimize risk of rabies disease. However, in very few cases development of rabies disease despite correct treatment has been reported. Direct inoculation of the rabies virus into nerve endings has been discussed as an explanation for these rare cases.

In very rare cases immediate-type allergic reactions may occur even after the first application of RABAVERT, e.g., when pre-sensitization occurred with a different product with similar excipients.

DRUG INTERACTIONS

Serious Drug Interactions

Radiation therapy, antimalarials, corticosteroids, other immunosuppressive agents and immunosuppressive illnesses can interfere with the development of active immunity after vaccination, and may diminish the protective efficacy of the vaccine.

Overview

Pre-exposure vaccination may be administered to persons under radiation therapy, antimalarials, corticosteroids, other immunosuppressive agents, and persons with immunosuppressive illnesses with the awareness that the immune response may be inadequate.

Immunosuppressive agents should not be administered during post-exposure prophylaxis unless essential for the treatment of other conditions. When rabies post-exposure prophylaxis is administered to persons receiving corticosteroids or other immunosuppressive therapy, or who are immunosuppressed, it is important that a serum sample on Day 14 (the day of the fourth vaccination) be tested for rabies antibody to ensure that an acceptable antibody response has been induced (RFFIT).

RIG must not be administered at more than the recommended dose, and not later than eight days after administration of first RABAVERT (Rabies Vaccine) dose since active immunization to the vaccine may be impaired.

No clinical trial data are available regarding the concurrent administration of RABAVERT with other vaccines. Other essential inactivated vaccines may be given at the same time as RABAVERT. Different injectable inactivated vaccines should be administered into separate injection sites and preferably different limbs. The vaccine must not be mixed in the same syringe with other medicinal products.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Pre-exposure vaccination - primary series and booster doses.
- Post-exposure prophylaxis.

Recommended Dose and Dosage Adjustment

The individual dose for adults, children, and infants is 1 mL, given intramuscularly.
In adults and children 2 years of age and above, administer RABAVERT (Rabies Vaccine) by IM injection into the **deltoid muscle**. In small children and infants (below 2 years of age), administer vaccine into the anterolateral zone of the thigh. The gluteal area should be avoided for vaccine injections, since administration in this area may result in lower neutralizing antibody titres.

Care should be taken to avoid injection into or near blood vessels and nerves. After aspiration, if blood or any suspicious discoloration appears in the syringe, do not inject but discard contents and repeat procedure using a new dose of vaccine, at a different site.

Pre-Exposure Dosage

Primary Immunization

Three intramuscular injections of 1.0 mL each:

One injection on each of **Days 0, 7, and 21 (or 28)**.

Healthy people immunized with an appropriate regimen will develop rabies antibodies, and therefore routine post-immunization antibody determinations are not recommended. Neutralizing antibodies develop 7 days after the second dose of primary immunization and persist for at least 2 years after the third dose.

The Canadian national rabies reference laboratory considers an acceptable antibody response to be a titre of ≥ 0.5 IU/mL by the Rapid Fluorescent-Focus Inhibition Test (RFFIT). Post-immunization antibody titre determination may be advisable for those anticipating frequent exposure or whose immune response may be reduced by illness, medication or advanced age.

Booster Immunization

The individual booster dose is 1 mL, given intramuscularly.

People with continuing high risk of exposure, such as certain veterinarians, should have their serum tested for rabies antibodies every 2 years (RFFIT); others working with live rabies virus in laboratories or vaccine production facilities who are at risk of unapparent exposure should be tested every 6 months.

Those with inadequate titres should be given a booster dose of RABAVERT.

Alternatively, booster doses may be given every 2-5 years, if situation does not warrant continual serological control and depending on the level of exposure risk.

Post-Exposure Dosage for Previously Unvaccinated Persons

Immunization should begin as soon as possible after exposure. A complete course of immunization consists of a total of 5 injections of 1 mL each:

One injection on each of **Days 0, 3, 7, 14 and 28.**

In conjunction with the administration of human rabies-specific immunoglobulin (RIG) on Day 0. Other immunization schedules have also been validated by the World Health Organization (WHO).

Post-exposure prophylaxis should be started as soon as possible after exposure and should be offered to exposed individuals regardless of the elapsed interval. If the suspect animal is domestic and is available for quarantine, then immunization may be withheld pending the animal's status after the 10-day observation period. However, if the bite wound is to the head and neck region, prophylaxis should begin immediately and not be delayed until after the 10-day period. When notification of an exposure is delayed, prophylaxis may be started as late as 6 or more months after exposure.

Begin with the administration of (human) RIG. Give 20 IU/kg body weight. This formula is applicable to all age groups, including infants and children. The recommended dosage of human RIG should not exceed 20 IU/kg body weight as it may otherwise interfere with active antibody production. For both human and non-human RIG administration and dosage, please refer to package information leaflet of respective product.

Since vaccine-induced antibody appears within 1 week, RIG is not indicated more than 8 days after initiating post-exposure prophylaxis with RABAVERT. If anatomically feasible, the full dose of RIG should be thoroughly infiltrated in the area around and into the wounds. Any remaining volume of RIG should be injected IM at a site distant from rabies vaccine administration. RIG should never be administered in the same syringe or in the same anatomical site as the rabies vaccine.

Because the antibody response following the recommended immunization regimen with RABAVERT has been satisfactory, routine post-immunization serologic testing is not recommended. Serologic testing is indicated in unusual circumstances, as when the patient is known to be immunosuppressed (RFFIT).

Post-Exposure Dosage for Previously Immunized Persons

When rabies exposure occurs in a **previously vaccinated** person, that person should receive two IM (deltoid) doses (1.0 mL each) of RABAVERT:

One injection on **Day 0 (immediately after exposure) and Day 3**.

RIG should not be given in these cases. Persons considered to have been immunized previously are those a) who received a complete pre-exposure vaccination or post-exposure prophylaxis with RABAVERT or other tissue culture vaccines; or b) who have been documented to have had a protective antibody response to another rabies vaccine or to unapproved schedules or routes of administration. If the immune status of a previously vaccinated person is not known, full post-exposure antirabies prophylaxis (RIG plus 5 doses of vaccine) is recommended. In such cases, if protective levels of neutralizing antibodies can be demonstrated in a serum sample collected before vaccine is given (RFFIT), treatment can be discontinued after at least two doses of vaccine.

Administration

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 package contains a vial of lyophilized powder, a syringe containing 1mL of diluent-and two identical sterile needles, one for reconstitution and one for intramuscular injection.. Affix one of the needles to the syringe containing the Sterile Diluent for RABAVERT. Insert the needle at a 45° angle and slowly inject the entire contents of the diluent (1 mL) into the vaccine vial. Mix gently to avoid foaming. The white, lyophilized powder dissolves to give a clear to slightly opalescent, colourless to slightly pink solution. Withdraw the total amount of dissolved vaccine into the syringe by inverting the vial and pulling the needle back close to the stopper. This will allow the full amount of vaccine solution to be withdrawn from the vial. Replace the needle used for reconstitution with the second needle for IM injection. The reconstituted vaccine should be used immediately.

A separate, sterile syringe and needle must be used for each patient. Needles must not be recapped and should be properly disposed of (see SPECIAL HANDLING INSTRUCTIONS section).

The lyophilization of the vaccine is performed under reduced pressure and the subsequent closure of the vials is done under vacuum. If there is no negative pressure in the vial, injection of Sterile Diluent for RABAVERT would lead to an excess positive pressure in 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 may prevent withdrawing the proper amount of the vaccine.

Vial	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
1 vial of Lyophilized powder containing a single dose	1 mL	1 mL	≥ 2.5 IU/mL of rabies antigen

OVERDOSAGE

Insufficient data are available.

For Management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Intramuscular injection of RABAVERT (Rabies Vaccine) induces lymphocytes to produce virus neutralizing antibodies that provide adequate protection against rabies virus.

Pharmacodynamics

Pre-Exposure Vaccination

The immunogenicity of RABAVERT has been demonstrated in clinical trials conducted in Europe, North America and Asia. When administered according to the recommended immunization schedule (Days 0, 7, 21 or 28), 100% of subjects attained an adequate titre of 0.5 IU/mL by Day 28 or earlier. Persistence of antibody titres ≥ 0.5 IU/mL for up to 2 years after immunization of RABAVERT has been measured in clinical trials.

Pre-Exposure Vaccination in Children

Pre-exposure administration of RABAVERT in 11 Thai children from the age of 2 years and older resulted in antibody levels higher than 0.5 IU/mL on Day 14 in all children.

Post-Exposure Prophylaxis

Clinical studies in patients exposed to rabies virus have demonstrated that RABAVERT, when used in the recommended post-exposure World Health Organization (WHO) schedule of 5 to 6 IM injections of 1 mL (on Days 0, 3, 7, 14, 28), provided protective titres of neutralizing antibodies (> 0.5 IU/mL) in 98% of patients within 14 days and in 100% of patients by Day 30.

Similar results were obtained in several studies with healthy volunteers who had been given the WHO recommended post-exposure regimen ("simulated" post-exposure immunization).

Failures have occurred, almost always after deviation from the recommended post-exposure prophylaxis protocol. However, in very few cases development of rabies disease despite correct treatment has been reported. Direct inoculation of the rabies virus into nerve endings has been discussed as an explanation for these rare cases.

Post-Exposure Prophylaxis in Children

In a 10-year serosurveillance study, RABAVERT has been administered to 91 children aged 1 to 5 years and 436 children and adolescents aged 6 to 20 years. The vaccine was effective in both age groups. None of these patients developed rabies.

Pharmacokinetics

Not applicable.

STORAGE AND STABILITY

RABAVERT (Rabies Vaccine) should be stored protected from light at 2°C to 8°C. After reconstitution, the vaccine is to be used immediately. The vaccine may not be used after the expiration date given on package and container.

SPECIAL HANDLING INSTRUCTIONS

RABAVERT (Rabies Vaccine) is a white, lyophilized powder for reconstitution with the water for injection diluent prior to use; the reconstituted vaccine is a clear to slightly opalescent, colorless to slightly pink solution.

RABAVERT 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 DESCRIPTION section.

The powder for solution should be reconstituted using the diluent 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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition

Single dose (1 mL) RABAVERT (rabies vaccine) contains: ≥2.5 IU of rabies antigen.

Excipients: disodium edetate 0.2-0.3 mg, hydrogen chloride, polygeline 9.0-12.0 mg, potassium-L-glutamate 0.8-1.0 mg, sodium chloride 4.0-5.0 mg, sucrose 20.0-100.0 mg, trometamol 3.0-4.0 mg, water for injection.

Residues from the manufacturing process: amphotericin B, chlortetracycline, human serum albumin, neomycin, and ovalbumin.

Packaging

1 vial of lyophilized powder containing a single dose
1 disposable pre-filled syringe of Sterile Diluent for RABAVERT (Rabies Vaccine) (1 mL)
2 identical 25 gauge x 1" needles – one for reconstitution and one for administration

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Rabies vaccine
Chemical name:	Not applicable
Molecular formula and molecular mass:	Not applicable
Structural formula:	Not applicable
Physicochemical properties:	Not applicable

Product Characteristics

RABAVERT, Rabies Vaccine, is a sterile lyophilized powder obtained by growing the fixed-virus strain Flury LEP in primary cultures of chicken fibroblasts. The strain Flury LEP was obtained from American Type Culture Collection as the 59th egg passage. The growth medium for propagation of the virus is a synthetic cell culture medium with the addition of human albumin, polygeline (processed bovine gelatin) and antibiotics.

The virus is inactivated with beta-propiolactone, and further processed by zonal centrifugation in a sucrose density-gradient. The vaccine is lyophilized after addition of a stabilizer solution which consists of buffered polygeline and potassium glutamate. One dose of reconstituted vaccine contains ≤12 mg polygeline (processed bovine gelatin), ≤0.3 mg human serum albumin, 1 mg potassium-L-glutamate, and 0.3 mg disodium edetate. Small quantities of bovine serum are used in the cell culture process. Bovine components originate only from source countries known to be free of bovine spongiform encephalopathy. Minimal amounts of chicken protein may be present in the final product; ovalbumin content is ≤3 ng/dose (1 mL), based on ELISA. Antibiotics (neomycin, chlortetracycline, amphotericin B) added during cell and virus propagation are largely removed during subsequent steps in the manufacturing process. In the final vaccine, neomycin is present at ≤10 mcg, chlortetracycline at ≤200 ng, and amphotericin B at ≤20 ng per dose.

RABAVERT is intended for intramuscular (IM) injection. The vaccine contains no preservative and should be used immediately after reconstitution with the supplied Sterile Diluent for RABAVERT (Water for Injection).

The potency of the final product is determined by the NIH mouse potency test using the US reference standard. The potency of one dose (1.0 mL) RABAVERT is at least 2.5 IU of rabies antigen.

RABAVERT is a white, lyophilized powder for reconstitution with the diluent prior to use. The reconstituted vaccine is a clear to slightly opalescent, colorless to slightly pink solution.

Viral Inactivation

Only human serum albumin (HSA) approved for sale in Canada is used for the production of RABAVERT. Therefore, the HSA complies with the requirements of the USP regarding viral inactivation.

CLINICAL TRIALS

Pre-Exposure Vaccination

The immunogenicity of RABAVERT has been demonstrated in clinical trials conducted in different countries such as the USA[1,2], Croatia[3], UK[4], and Thailand[5,6]. When administered according to the recommended immunization schedule (Days 0, 7, 21 or Days 0, 7, 28), 100% of subjects attained protective titres. In two single-blind, randomized, controlled studies carried out in the USA in 101 subjects, antibody titres > 0.5 IU/mL were obtained by Day 28 in all subjects[1,2]. In a double-blind, randomized, controlled study carried out in Croatia[3] in 25 subjects, in a randomized, controlled study carried out in the UK[4] in 15 subjects, and in an uncontrolled study in Thailand[5,6] in 22 subjects, antibody titres of > 0.5 IU/mL were obtained by Day 14 (injections on Days 0, 7, 21) in all subjects.

The ability of RABAVERT to boost previously immunized subjects was evaluated as a follow-up to four blinded, randomized, controlled clinical trials[1,2,7,8]. In a U.S. study, one or two booster

doses were administered to 140 individuals approximately one year after a three-dose pre-exposure vaccination series. Antibody titres of > 0.5 IU/mL were present before the booster dose in all subjects[2]. Titres were enhanced from geometric mean titres (GMT) of 2.33 IU/mL before the booster dose to 51.23 IU/mL on Day 7 after one booster dose. Following two booster doses (Days 0, 3) titres were enhanced from 1.84 IU/mL to 51.67 IU/mL on Day 7[2].
In another booster study, individuals known to have been immunized with Human Diploid Cell Rabies Vaccine (HDCV) were boosted with RABAVERT approximately 4 years after primary immunization. In this study, a booster response was observed on Day 14 for all 22 individuals[7].

In the two booster trials carried out in the USA[1,2] and in a booster trial carried out in Croatia[8], a RABAVERT IM booster dose one, two or three years after primary immunization resulted in a more than 10-fold increase in GMTs, regardless of whether the subjects had received RABAVERT or HDCV as the primary vaccine.

Persistence of antibody after immunization with RABAVERT has been evaluated. In a single-blind, randomized, controlled trial performed in the UK, neutralizing antibody titres > 0.5 IU/mL were present 2 years after immunization in all 6 sera tested[4]. In another single-blind, randomized, controlled trial performed in the USA, a protective titre was present 2 years after immunization in all 19 subjects who received RABAVERT intramuscularly[1]. In a follow-up to this study adequate neutralizing antibody titres > 1:5, indicative for protection were present 14 years after a booster immunization in all 10 subjects tested. All of these subjects responded with a more than 10-fold increase to a single booster dose[9].

The immunogenicity of RABAVERT, when given intradermally in a pre-exposure regimen has been demonstrated in a clinical trial in Thailand. When intradermal doses of 0.1mL were administered according to the recommended immunization schedule (Days 0, 7, 21), by day 14 100% (n=24) of the subjects attained adequate titres ≥ 0.5IU/mL, although significantly higher titers were obtained in the IM group[10].

Pre-Exposure Vaccination in Children

Pre-exposure administration of RABAVERT in 11 Thai children from the age of 2 years and older resulted in antibody levels higher than 0.5 IU/mL on Day 14 in all children[11].

Post-Exposure Prophylaxis

RABAVERT, when used in the recommended post-exposure Centers for Disease Control (CDC) regimen of 5 IM injections of 1 mL (Days 0, 3, 7, 14 and 28) or WHO regimen of 5 to 6 IM injections of 1 mL (Days 0, 3, 7, 14, 30, and one optionally on Day 90) provides protective titres of neutralizing antibody. In studies conducted outside of the USA, 158/160 patients[5,6,12-15] by Day 14 and 215/216 patients by Day 28-38 produced antibody levels of > 0.5 IU/mL.

Of these, 203 were followed for at least 10 months. No case of rabies was observed[5,6,12-18]. Some patients received Human Rabies Immunoglobulin (HRIG), 20-30 IU per kg body weight, or Equine Rabies Immunoglobulin (ERIG), 40 IU per kg body weight, at the time of the first dose. In two studies[5,12], the addition of either HRIG or ERIG caused a slight decrease in GMTs which was neither clinically relevant nor statistically significant. In one study[15], patients

receiving HRIG had significantly lower ($p < 0.05$) GMTs on Day 14; however, again this was not clinically relevant. After Day 14 there was no statistically significant difference.
The results of several studies of normal volunteers receiving the post-exposure WHO regimen[7,19-21], i.e., "simulated" post-exposure, show that with sampling by Day 28-30, 205/208 vaccinees had protective titres > 0.5 IU/mL.

Failures have occurred abroad, almost always after deviation from the recommended post-exposure prophylaxis protocol[22-25]. However, in very few cases development of rabies disease despite correct treatment has been reported[26]. Direct inoculation of the rabies virus into nerve endings has been discussed as an explanation for these rare cases.

RABAVERT, when used in the WHO recommended intradermal post-exposure regimens (the Thai Red Cross 2-site post-exposure regimen of 2 ID injections of 0.1 mL (Days 0, 3, 7) and 1 ID injection on Days 28 and 90; or the 8-site post-exposure regimen of 8 ID injections of 0.1 mL on Day 0, 4 ID injections of 0.1 mL on Day 7 and 1 ID injection on Days 28 and 90) provides adequate titres of neutralizing antibody, as demonstrated in several clinical trials[27,28].

The efficacy of RABAVERT when given in the Thai Red Cross 2-site post-exposure regimen was demonstrated in a clinical trial in the Philippines. One hundred and thirteen subjects, bitten by laboratory proven rabid animals and treated with RABAVERT in combination with rabies immunoglobulin were followed for one year and all subjects were healthy and alive after one year[29].

Post-Exposure Prophylaxis in Children

In a 10-year serosurveillance study, RABAVERT has been administered to 91 children aged 1 to 5 years and 436 children and adolescents aged 6 to 20 years[16]. The vaccine was effective in both age groups. None of these patients developed rabies.

One newborn has received RABAVERT on an immunization schedule of Days 0, 3, 7, 14 and 30; the antibody concentration on Day 37 was 2.34 IU/mL. There were no clinically significant adverse events[30].

Study Demographics and Trial Design

Table 4 - Summary of patient demographics for clinical trials in specific indication

Study	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Pre-exposure					
Ref. 1	Single-blind, randomized, controlled	0, 7, 28 (IM or ID)	78 in total 59 ID	(21-37)	35 (45%) m 43 (55%) f
			19 IM (receiving PCECV)	23.6 (21-32)	8 (42%) m 11 (58%) f
Ref. 2	Single-blind, randomized, controlled	0, 7, 28 (IM only)	165 in total (83 receiving PCECV)	24.8 (20-49)	73 (44%) m 92 (56%) f
Booster					
Ref. 2	Blinded, randomized, controlled	One or two IM booster doses (Day 0 or Days 0 and 3)	140	25.4 (21-44)	59 (42%) m 81 (58%) f
Ref. 1	Single-blind, randomized, controlled	0, 7, 28 (IM or ID)	78 in total 59 ID	(21-37)	35 (45%) m 43 (55%) f
			19 IM (receiving PCECV)	23.6 (21-32)	8 (42%) m 11 (58%) f
Post-exposure					
Ref. 31	Randomized, controlled, two centers	0, 3, 7, 14, 30, 90 (IM, 1.0 mL)	211 in total	28.9 (2-78)	78 (37%) m 133 (63%) f
		0-0, 3-3, 7-7, 30, 90 (ID, 0.1 mL)	57 receiving PCECV intramuscularly	33.6 (5-66)	28 (49%) m 29 (51%) f
Ref. 4	Double-blind, randomized, single-center, controlled	2 IM doses on Day 0, 1 IM dose on Days 3 and 7	185 in total 93 receiving post-exposure regimen	(19-25)	All male
Ref. 16	uncontrolled	Days 0, 3, 7, 14, 30 and 90	56 patients after exposure to proven rabid animals	unknown	unknown

In the pivotal pre-exposure and booster studies[1,2], the study population consisted of healthy adult subjects, mostly between 18 and 30 years of age and balanced gender ratio (see Table 4). In the pivotal post-exposure studies[4,16,31], the study population consisted of either healthy adult volunteers receiving “simulated” post-exposure prophylaxis or patients exposed to suspect or proven rabid animals.

Study Results

Table 5 - Results of studies in specific indication

Primary endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
Pre-exposure		
Ref. 1	100% of subjects had virus neutralizing antibody (VNA) titers >0.5 IU/mL by Day 28	Active control: human diploid cell culture vaccine (HDCV) (Mérieux) 100% of subjects had VNA titers >0.5 IU/mL
Ref. 2	100% of subjects had VNA titers >0.5 IU/mL	Active control: HDCV (Mérieux) 100% of subjects had VNA titers >0.5 IU/mL
Booster		
Ref. 2	Antibody titers >0.5 IU/mL before the booster in all subjects increase in titers (GMT) from 2.33 IU/mL before booster to 51.23 IU/mL on Day 7 after 1 booster dose and from 1.84 IU/mL to 51.67 IU/mL after two booster doses	NA
Ref. 1	100% of subjects had VNA titers >0.5 IU/mL by Day 7 after booster	NA
Post-exposure		
Ref. 31	VNA titers > 0.5 IU/mL in all subjects by Day 14	Active control: IM administration of purified vero cell rabies vaccine PVRV (Aventis Pasteur) VNA titers > 0.5 IU/mL in all subjects by Day 14 ID administration of PCECV VNA titers > 0.5 IU/mL in all subjects by Day 14
Ref. 4	VNA titers > 0.5 IU/mL in all subjects by Day 14	Active control: HDCV (Institut Mérieux) no significant difference of PCECV to HDCV
Ref. 16	Mean antibody titer of 4.45 IU/mL after the last dose; 100 % survival after 19 to 24 months follow-up period	NA

DETAILED PHARMACOLOGY

Pharmacodynamics

The protective capacity of the PCEC-vaccine was evaluated in comparison with the HDC-vaccine of similar antigenicity. The laboratory models used for comparison included antibody induction in mice and monkeys, challenge of vaccinated mice and guinea pigs, and a post-exposure vaccination experiment in guinea pigs.

Antibody Induction

Antibody induction tests were performed in mice comparing PCEC vaccine and HDC vaccine lots of high potency. Comparisons were also made using lots of marginal potency. Detectable levels of antibody were seen by Day 14 after injection and no notable differences were seen between the two vaccine types nor between vaccines of low and high antigenicity.

Macaca fascicularis monkeys received either single or multiple injections of PCEC or HDC vaccine. Detectable antibody levels were seen by Day 7 in all animals irrespective of the vaccine used and the vaccination schedule (n=6 animals/group). On Day 30 comparable antibody levels were found in the groups receiving a single injection of either vaccine. The antibody levels on Day 30 were slightly higher with multiple injections when compared to a single dose injection of the vaccine.

Challenge

Complete protection was provided to guinea pigs vaccinated with either vaccine prior to peripheral intramuscular challenge with fixed virus strain CVS27. In mice the protection at the highest vaccine concentration was not as effective. Following intracerebral challenge with the CVS27 virus in mice only 56% of PCEC vaccinated animals and 62% of HDC vaccinated animals survived.

Post-Exposure

Guinea pigs were challenged with a dose of virus strain that normally killed 80% of the control animals with a mean incubation time of 8.5 days. Animals were treated with either the PCEC vaccine or the HDC vaccine 3 hours after challenge as well as daily for 4 additional days. In the treated animals 6/10 receiving the PCEC vaccine and 7/10 receiving the HDC vaccine survived with a mean survival time of 7.7-7.9 days. Both vaccines offered significant protection in terms of the actual numbers of survivors.

Street virus strain NYC at intramuscular doses (approximately 5 x LD_{50}) that killed 100% of the controls with a mean survival time of 16.5 days was used to challenge mice. Vaccine treatment was started either 3 hours or 24 hours after challenge. Groups of NMRI mice (n=16/group) received four daily vaccine injections followed by a fifth injection 24 or 72 hours later. The duration of the experiments was between 28 and 42 days. Better protection rates were achieved

when the vaccine treatment was begun 3 hours after challenge instead of 24 hours after challenge. In each of the five experiments performed, survival rates were higher with the PCEC vaccine than with the HDC vaccine. The percentage of survivors due to the PCEC vaccine varied from 50-93% with mean survival times of 13.0-18.0 days. Survival rates with the HDC vaccine varied from 19-75% with mean survival times of 12.5-15.7 days.

Post-exposure to PCEC vaccine or HDC vaccine treatment started 3 hours after low dose challenge with rabies virus strain CVS27, followed by an additional 4 daily vaccinations, resulted in a 50-56% survival rate of infected mice (n=16 mice/group). A suckling mouse brain vaccine offered only 25% survival rate. When the virus dose was increased by a factor of 10 the survival rate was 0% regardless of the vaccine used. The mean survival time of all groups varied from 7.0-7.6 days. The duration of the experiment was 28 days.

Pharmacokinetics

ADME (absorption, distribution, metabolism, excretion) studies were not performed because these studies are not required/relevant for this type of vaccine. The pharmacodynamic effects of the vaccine, the induction of protective antibodies, is described above.

TOXICOLOGY

Toxicity Studies

Toxicity testing of RABAVERT was performed with the final preparation of the vaccine. Performance of toxicity testing, including selection of animal models and dose levels/regimens, represent the scientific and regulatory standards of testing vaccines.

Table 6 – Toxicity studies

Toxicology study	Animal	N	Dose level	Result summary
Single dose toxicity	Mice	10 m 10 f	0.25 mL, 0.5 mL, 1.0 mL	All animals survived. Body weight gain was comparable to the control animals. The vaccine was subcutaneously well tolerated up to and including the dose for humans.
	Rats	10 m 10 f	0.25 mL, 0.5 mL, 1.0 mL	All animals survived. Body weight gain was comparable to the control animals. The vaccine was subcutaneously well tolerated up to and including the dose for humans.
	Rabbits	4 m 4 f	Placebo 1.0 mL	All animals survived. The vaccine was intramuscularly and systemically well tolerated at the human dose.
Repeated dose toxicity	Rabbits	6 m 6 f	Placebo 1.0 mL	All animals survived. The vaccine was immunogenic and was intramuscularly and systemically well tolerated at the human dose administered 5 times (dosing every 2 weeks). Findings of reversibly elevated fibrinogen and reversible inflammatory infiltrates at the injection sites were consistent with the administration of an immunogenic vaccine.
	Dogs	2 m 2 f	1.0 mL (5.0 IU)	All animals survived. Body weight gain was comparable to the control animals. No adverse effects were noted in general condition or behavior. No evidence of toxicity to the vaccine was seen.
	Monkeys	6 m – one dose 6 f – one dose 5 m – repeat dose 7 f – repeat dose	3.5 IU PCEC vaccine, 3.5 IU HDC vaccine	There was no treatment-related mortality or effects on clinical signs or body weights. In the single-dose part of the study there were sporadic elevations in liver function tests (AST and/or ALT) in individual animals. Because these parameters were not affected by repeat administration, these findings were considered unlikely to be related to the vaccines. The test vaccines demonstrated little, if any, toxicity after either single or repeated injections.

Local Tolerance

An intramuscular local tolerance study was performed in rabbits. A 0.5mL quantity (1.25IU) was injected intramuscularly, and the sites were evaluated histologically and compared to sites in which 0.5 mL of the stabilizing agent had been injected. Microscopically, the vaccine and stabilizer sites were similar. Mild inflammatory changes were seen on the second day and resolution of these changes were evident by the fifth day. It was concluded that the vaccine was locally well tolerated. Local intramuscular tolerability was also assessed in the single and repeated-dose rabbit toxicology studies. The local reactogenicity was also of a low order of magnitude following 5 intramuscular doses.

In addition, an intracutaneous tolerance study was performed in rabbits dosed with 0.1 mL (0.25 IU) of the vaccine. The thickness of vaccine-treated injection sites were compared to the isotonic saline treated (control) injection sites daily until necropsy on Day 8. A slight increase in skin fold thickness was observed between Days 7 and 8. Cellular infiltrations were found at injection sites at a somewhat higher degree in the vaccinated animals. It was concluded that the vaccine provoked local inflammation after intracutaneous injection.

In conclusion, in single- and repeated-dose nonclinical studies with clinically-relevant doses in several small and large animal species, RABAVERT was immunogenic and protective and was systemically and locally well tolerated.

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PART III: CONSUMER INFORMATION

RABAVERT
Rabies vaccine

This leaflet is part III of a three-part "Product Monograph" published when RABAVERT was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about RABAVERT. Contact your doctor or pharmacist if you have any questions about the vaccine.

ABOUT THIS VACCINE

What the vaccine is used for:

RABAVERT is indicated for:

- Pre-exposure vaccination, in both primary series and booster doses against rabies in all age groups.
- Post-exposure prophylaxis against rabies in all age groups.

What it does:
Intramuscular injection of RABAVERT induces lymphocytes to produce virus neutralizing antibodies that provide adequate protection against rabies virus.

When it should not be used:
In view of the almost invariably fatal outcome of rabies, there is no contraindication to post-exposure prophylaxis, including pregnancy.

History of anaphylaxis to the vaccine or any of the vaccine components, including the container, constitutes a contraindication to pre-exposure vaccination with this vaccine.

If you have an acute infection. The presence of a minor infection, such as a cold, should not require postponement of the pre-exposure vaccination, but talk to your doctor or nurse first.

What the medicinal ingredient is:
Rabies vaccine

What the nonmedicinal ingredients are:
Disodium edetate, hydrogen chloride, polygeline, potassium-L-glutamate, sodium chloride, sucrose, trometamol, water for injection. Residues from the manufacturing process: Amphotericin B, chlortetracycline, human serum albumin, neomycin, and ovalbumin.

What dosage forms it comes in:
RABAVERT is available as:
1 vial of lyophilized powder containing a single dose; and,
1 disposable pre-filled syringe of Sterile Diluent for RABAVERT (1 mL), with needles.

RABAVERT has at least 2.5 IU of rabies antigen.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Anaphylaxis and neuroparalytic events such as encephalitis, transient paralysis and Guillain-Barré-Syndrome, have been reported to be temporally associated with the use of RABAVERT. A patient's risk of developing rabies must be carefully considered, however, before deciding to discontinue immunization.

RABAVERT MUST NOT BE USED SUBCUTANEOUSLY AND SHOULD NOT BE USED INTRADERMALLY.

DO NOT INJECT INTRAVASCULARLY.

BEFORE you use RABAVERT talk to your physician or pharmacist if:

- You are under radiation therapy, antimalarials, corticosteroids, or other immunosuppressive agents.
- You are a person with immunosuppressive illnesses.
- You are allergic to this drug or its ingredients or components of the container.
- You have fainted with a previous injection. Fainting can occur following, or even before, any needle injection.
- You are or think you may be pregnant, you may still be given rabies vaccine if you have had, or are likely to have had, contact with the virus. If the risk

of contact with the virus is thought to be considerable, your doctor will advise you whether to have rabies vaccine now or to wait.
- You are breastfeeding. You can receive RABAVERT if the risk of contact with the virus is thought to be considerable. Your doctor will advise you.

As with all vaccines, RABAVERT may not fully protect all people who are vaccinated.

INTERACTIONS WITH THIS VACCINE

Drugs that may interact with RABAVERT include:
- Antimalarials
- Corticosteroids
- Immunosuppressive agents

RABAVERT can be given at the same time as other vaccines. A different injection site will be used for each type of vaccine.

You may also need to be given an injection of antibodies against rabies (called "rabies immunoglobulin"). If so, the rabies immunoglobulin injection will be given in different limbs.

PROPER USE OF THIS VACCINE

Usual dose:
A. Primary Immunization (Pre-exposure vaccination)

Three intramuscular injections of 1.0 mL each:
One injection on each of **Days 0, 7, and 21 (or 28)**

B. Booster Immunization

The individual booster dose is 1 mL, given intramuscularly.

C. Post-Exposure Prophylaxis

A complete course of immunization consists of a total of 5 injections of 1 mL each:
One injection on each of **Days 0, 3, 7, 14 and 28**
In conjunction with the administration of rabies immunoglobulin (RIG) on Day 0.

D. Post-Exposure Prophylaxis of Previously Immunized Persons

When rabies exposure occurs in a previously vaccinated person, then that person should receive two IM (deltoid) doses (1.0 mL each) of RABAVERT:
One dose immediately and one 3 days later.
Human Rabies Immunoglobulin (RIG) should not be given in these cases.

Missed Dose:
Please refer to your physician in case of a missed vaccination.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects reported can be:
- Very common (these may affect more than 1 in 10 people);
- Common (these may affect up to 1 in 10 people);
- Uncommon (these may affect up to 1 in 100 people);
- Rare (these may affect up to 1 in 1,000 people); or,
- Very rare (these may affect less than 1 in 10,000 people).

In very rare cases, neurological events such as those in the Serious Warnings and Precautions section above and other severe conditions affecting the brain and nerves have been reported in temporal association with administration of RABAVERT. Consult your physician if you experience any of these mentioned cases.

Your risk of developing rabies must be carefully considered, however, before deciding to discontinue immunization.

The most commonly occurring adverse reactions are injection-site reactions - such as swelling and pain; flu-like symptoms - such as fatigue, fever, headache, dizziness, weakness, and rash, that may also be red, lumpy, itchy (very common); injection-site redness, abdominal pain, lymph node swelling, muscle pain and general discomfort, joint pain, nausea, vomiting, diarrhea, and decreased appetite (common).

In rare cases, chills and sweating, circulatory reactions – such as hot flush - visual disturbance, tingling or numbness of skin, pain in limbs, feeling faint, fainting, and hypersensitivity have been reported.

Serious allergic reactions are rare after receiving a vaccine. These reactions may include:
• difficulty in breathing,
• blue discolouration of the tongue or lips,
• swelling of the face and neck or elsewhere
• low blood pressure causing collapse and shock.
When these signs or symptoms occur, they usually develop very quickly after the injection is given; consult a doctor immediately.

Once initiated, rabies prophylaxis should not be interrupted or discontinued because of local or mild general adverse reactions to rabies vaccine. Usually such reactions subside within a few days and may be successfully managed with anti-inflammatory and fever reducing agents.

This is not a complete list of side effects. For any unexpected effects while taking RABAVERT*, contact your physician or pharmacist.*

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following immunization.

For health care professionals:
If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local Health Unit in your province/territory.

For the General Public:
Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.

If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada:

By toll-free telephone: 866-844-0018
By toll-free fax: 866-844-5931
By email: caefi@phac-aspc.gc.ca
At the following website:
http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php

By regular mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road
Ottawa, Ontario
K1A 0K9 Address Locator 6502A

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

HOW TO STORE IT

RABAVERT should be stored protected from light at 2°C to 8°C. After reconstitution, the vaccine is to be used immediately. The vaccine may not be used after the expiration date given on package and container.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
www.bnvaccines.ca
or by contacting the manufacturer:
medical.information_NA@bavarian-nordic.com or by calling 1-833-203-7933

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