

## 54555750RabAvert®

### Rabies Vaccine

### Rabies Vaccine for Human Use

#### Description

RabAvert, Rabies Vaccine, produced by Novartis Vaccines and Diagnostics GmbH is a sterile freeze-dried vaccine 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 less than 12 mg polygeline (processed bovine gelatin), less than 0.3 mg human serum albumin, 1 mg potassium glutamate and 0.3 mg sodium EDTA. Small quantities of bovine serum are used in the cell culture process. Bovine components originate only from the United States, Australia and New Zealand. Minimal amounts of chicken protein may be present in the final product; ovalbumin content is less than 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  $< 1 \mu\text{g}$ , chlortetracycline at  $< 20 \text{ ng}$ , and amphotericin B at  $< 2 \text{ ng}$  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, freeze-dried vaccine for reconstitution with the diluent prior to use; the reconstituted vaccine is a clear to slightly opaque, colorless suspension.

#### Clinical Pharmacology

##### Rabies in the United States

Over the last 100 years, the epidemiology of rabies in animals in the United States has changed dramatically. More than 90% of all animal rabies cases reported annually to the Centers for Disease Control and Prevention (CDC) now occur in wildlife, whereas before 1960 the majority were in domestic animals. The principal rabies hosts today are wild terrestrial carnivores and bats. Annual human deaths have fallen from more than a hundred at the turn of the century to one to two per year despite major epizootics of animal rabies in several geographic areas. Within the United States, only Hawaii has remained rabies free. Although rabies among humans is rare in the United States, every year tens of thousands of people receive rabies vaccine for postexposure prophylaxis.

Rabies is a viral infection transmitted via the saliva of infected mammals. The virus enters the central nervous system of the host, causing an encephalomyelitis that is almost invariably fatal. The incubation period varies between 5 days and several years, but is usually between 20 and 60 days. Clinical rabies presents either in a furious or in a paralytic form. Clinical illness most often starts with prodromal complaints of malaise, anorexia, fatigue, headache, and fever followed by

50 pain or paresthesia at the site of exposure. Anxiety, agitation, irritability may be prominent  
52 during this period, followed by hyperactivity, disorientation, seizures, aero- and hydrophobia,

54 hypersalivation, and eventually paralysis, coma and death.  
56 Modern day prophylaxis has proven nearly 100% successful; most human fatalities now occur in  
58 people who fail to seek medical treatment, usually because they do not recognize a risk in the  
60 animal contact leading to the infection. Inappropriate postexposure prophylaxis may also result  
62 in clinical rabies. Survival after clinical rabies is extremely rare, and is associated with severe  
64 brain damage and permanent disability.

58 RabAvert (in combination with passive immunization with Human Rabies Immune Globulin  
60 [HRIG] and local wound treatment) in postexposure treatment against rabies has been shown to  
62 protect patients of all age groups from rabies, when the vaccine was administered according to the  
64 CDC's Advisory Committee on Immunization Practices (ACIP) or World Health Organization  
66 (WHO) guidelines and as soon as possible after rabid animal contact. Anti-rabies antibody titers  
68 after immunization have been shown to reach levels well above the minimum antibody titer  
accepted as seroconversion (protective titer) within 14 days after initiating the postexposure  
treatment series. The minimum antibody titer accepted as seroconversion is a 1:5 titer (complete  
inhibition in the rapid fluorescent focus inhibition test [RFFIT] at 1:5 dilution) as specified by the  
CDC (1), or  $\geq 0.5$  IU per milliliter (mL) as specified by the WHO (2,3).

### Clinical Studies

#### Preexposure Vaccination

70 The immunogenicity of RabAvert has been demonstrated in clinical trials conducted in different  
72 countries such as the USA (4,5), UK (6), Croatia (7), and Thailand (8-10). When administered  
74 according to the recommended immunization schedule (days 0, 7, 21 or 0, 7, 28), 100% of  
76 subjects attained a protective titer. In two studies carried out in the USA in 101 subjects, antibody  
titers  $> 0.5$  IU/mL were obtained by day 28 in all subjects. In studies carried out in Thailand in 22  
subjects, and in Croatia in 25 subjects, antibody titers of  $> 0.5$  IU/mL were obtained by day 14  
(injections on days 0, 7, 21) in all subjects.

78 The ability of RabAvert to boost previously immunized subjects was evaluated in three clinical  
80 trials. In the Thailand study, preexposure booster doses were administered to 10 individuals.  
82 Antibody titers of  $> 0.5$  IU/mL were present at baseline on day 0 in all subjects (9). Titers after a  
booster dose were enhanced from geometric mean titers (GMT) of 1.91 IU/mL to 23.66 IU/mL  
on day 30. In an additional booster study, individuals known to have been immunized with  
Human Diploid Cell Vaccine (HDCV) were boosted with RabAvert. In this study, a booster  
response was observed on day 14 for all (22/22) individuals (11). In a trial carried out in the USA  
(4), a RabAvert IM booster dose resulted in a significant increase in titers in all (35/35) subjects,  
regardless of whether they had received RabAvert or HDCV as the primary vaccine.

86 Persistence of antibody after immunization with RabAvert has been evaluated. In a trial  
88 performed in the UK, neutralizing antibody titers  $> 0.5$  IU/mL were present 2 years after  
immunization in all sera (6/6) tested.

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#### Preexposure Vaccination in Children

92 Preexposure administration of RabAvert in 11 Thai children from the age of 2 years and older  
94 resulted in antibody levels higher than 0.5 IU/mL on day 14 in all children (12).

96 Postexposure Treatment

98 RabAvert, when used in the recommended postexposure WHO program of 5 to 6 IM injections of  
100 1 mL (days 0, 3, 7, 14, 30, and one optionally on day 90) provided protective titers of neutralizing  
antibody (> 0.5 IU/mL) in 158/160 patients (8, 9, 13-16) within 14 days and in 215/216 patients  
by day 28 - 38.

102 Of these, 203 were followed for at least 10 months. No case of rabies was observed (8, 9, 13-20).  
Some patients received Human Rabies Immune Globulin (HRIG), 20 - 30 IU per kg body weight,  
104 or Equine Rabies Immune Globulin (ERIG), 40 IU per kg body weight, at the time of the first  
dose. In most studies (8, 9, 13, 17), the addition of either HRIG or ERIG caused a slight decrease  
106 in GMTs which was neither clinically relevant nor statistically significant. In one study (16),  
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 statistical significance.

108 The results of several studies of normal volunteers receiving the postexposure WHO regimen,  
i.e., "simulated" postexposure, show that with sampling by day 28 - 30, 205/208 vaccinees had  
110 protective titers > 0.5 IU/mL.

112 No postexposure vaccine failures have occurred in the United States since cell culture vaccines  
have been routinely used (1). Failures have occurred abroad, almost always after deviation from  
114 the recommended postexposure treatment protocol (21-24). In two cases with bites to the face,  
treatment failed although no deviation from the recommended postexposure treatment protocol  
116 appeared to have occurred (25).

Postexposure Treatment in Children

118 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 (19). The vaccine was effective in  
120 both age groups. None of these patients developed rabies.

122 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  
124 events (26).

## Indications and Usage

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RabAvert is indicated for preexposure vaccination, in both primary series and booster dose, and for postexposure prophylaxis against rabies in all age groups.

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Usually, an immunization series is initiated and completed with one vaccine product. No clinical studies have been conducted that document a change in efficacy or the frequency of adverse reactions when the series is completed with a second vaccine product. However, for booster immunization, RabAvert was shown to elicit protective antibody level responses in persons tested who received a primary series with HDCV (4,11).

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### A. Preexposure Vaccination - See Table 1

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(see also **Dosage and Administration** section below)

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Preexposure vaccination consists of three doses of RabAvert 1.0 mL, intramuscularly (deltoid region), one each on days 0, 7, and 21 or 28 (1) (see also Table 1 for criteria for preexposure vaccination).

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Preexposure vaccination does not eliminate the need for additional therapy after a known rabies exposure (see also **Dosage and Administration** section, subsection C).

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Preexposure vaccination should be offered to persons in high-risk groups, such as veterinarians, animal handlers, wildlife officers in areas where animal rabies is enzootic, certain laboratory workers, and persons spending time in foreign countries where rabies is endemic. Persons whose activities bring them into contact with potentially rabid dogs, cats, foxes, skunks, bats, or other species at risk of having rabies should also be considered for preexposure vaccination. International travelers might be candidates for preexposure vaccination if they are likely to come in contact with animals in areas where dog rabies is enzootic and immediate access to appropriate medical care, including biologics, might be limited (27, 28)

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Preexposure vaccination is given for several reasons. First, it may provide protection to persons with inapparent exposure to rabies. Second, it may protect persons whose postexposure therapy might be expected to be delayed. Finally, although it does not eliminate the need for prompt therapy after a rabies exposure, it simplifies therapy by eliminating the need for globulin and decreasing the number of doses of vaccine needed. This is of particular importance for persons at high risk of being exposed in countries where the available rabies immunizing products may carry a higher risk of adverse reactions.

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In some instances, booster doses of vaccine should be administered to maintain a serum titer corresponding to at least complete neutralization at a 1:5 serum dilution by the RFFIT (see Table 1); each booster immunization consists of a single dose. See **Clinical Pharmacology**. Serum antibody determinations to decide upon the need for a booster dose is suggested by the ACIP and is considered cost-effective.

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164 **TABLE 1: RABIES PREEXPOSURE PROPHYLAXIS GUIDE – UNITED STATES,**  
 166 **1999**

<u>Risk Category and Nature of Risk</u>	<u>Typical Populations</u>	<u>Preexposure Recommendations</u>
<u>Continuous.</u> Virus present continuously, often in high concentrations. Specific exposures likely to go unrecognized. Bite, nonbite or aerosol exposure.	Rabies research lab workers,* rabies biologics production workers.	Primary course. Serologic testing every 6 months; booster vaccination if antibody titer is below acceptable level.*
<u>Frequent.</u> Exposure usually episodic, with source recognized, but exposure might be unrecognized. Bite, nonbite or aerosol exposure.	Rabies diagnostic lab workers,* spelunkers, veterinarians and staff, and animal-control and wildlife workers in rabies enzootic areas.	Primary course. Serologic testing every 2 years; booster vaccination if antibody titer is below acceptable level.**
<u>Infrequent</u> (greater than population-at-large). Exposure nearly always episodic with source recognized. Bite or nonbite exposure.	Veterinarians and animal-control and wildlife workers in areas with low rabies rates. Veterinary students. Travelers visiting areas where rabies in enzootic and immediate access to appropriate medical care including biologics is limited.	Primary course. No serologic testing or booster vaccination.**
<u>Rare</u> (population-at-large). Exposures always episodic with source recognized. Bite or nonbite exposure.	US population-at-large, including persons in rabies-epizootic areas.	No vaccination necessary.

168 Adapted from the Recommendations of the Advisory Committee on Immunization Practices: Human Rabies Prevention – United States, 1999. (1)

170 \* Judgment of relative risk and extra monitoring of vaccination status of laboratory workers is the responsibility of the laboratory supervisor (29).

172 \*\* Minimum acceptable antibody level is complete virus neutralization at a 1:5 serum dilution by RFFIT. A booster dose should be administered if the titer falls below this level.

174 ***B. Postexposure Treatment - See Table 2***

(see also **Dosage and Administration** section below)

176 The following recommendations are only a guide. In applying them, take into account the animal species involved, the circumstances of the bite or other exposure, the immunization status of the animal, and presence of rabies in the region (as outlined below). Local or state public health officials should be consulted if questions arise about the need for rabies prophylaxis (1).

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**TABLE 2: RABIES POSTEXPOSURE PROPHYLAXIS GUIDE – UNITED STATES, 1999**

Animal type	Evaluation and disposition of animal	Postexposure prophylaxis recommendations
Dogs, cats and ferrets	Healthy and available for 10 days observation	Should not begin prophylaxis unless animal develops clinical signs of rabies*
	Rabid or suspected rabid	Immediately vaccinate
	Unknown (e.g., escaped)	Consult public health officials
Skunks, raccoons, bats, foxes, and most other carnivores	Regarded as rabid unless animal proven negative by laboratory tests**	Consider immediate vaccination
Livestock, small rodents, lagomorphs (rabbits and hares), large rodents (woodchucks and beavers), and other mammals	Consider individually	Consult public health officials. Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other small rodents, rabbits, and hares almost never require antirabies postexposure prophylaxis

184 Adapted from the Recommendations of the Advisory Committee on Immunization Practices: Human Rabies Prevention – United States, 1999. (1)

186 \* During the 10-day observation period, begin postexposure prophylaxis at the first sign of rabies in a  
188 dog, cat or ferret that has bitten someone. If the animal exhibits clinical signs of rabies, it should be  
euthanized immediately and tested.

190 \*\* The animal should be euthanized and tested as soon as possible. Holding for observation is not  
recommended. Discontinue vaccine if immunofluorescence test results of the animal are negative.

192 In the United States, the following factors should be considered before antirabies treatment is  
initiated.

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#### Species of Biting Animal

196 Wild terrestrial animals (especially skunks, raccoons, foxes and coyotes) and bats are the animals  
most commonly infected with rabies and are the most important potential source of infection for  
198 both humans and domestic animals. Unless a wild animal is tested and shown not to be rabid,  
postexposure prophylaxis should be initiated upon bite or nonbite exposure to the animals (see  
200 definition in "Type of Exposure" below). If treatment has been initiated and subsequent testing in  
a qualified laboratory shows the exposing animal is not rabid, postexposure prophylaxis can be  
202 discontinued (1).

204 The likelihood of rabies in a domestic animal varies from region to region; hence the need for  
postexposure prophylaxis also varies (1).

206 Small rodents (such as squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, and mice) and  
lagomorphs (including rabbits and hares) are almost never found to be infected with rabies and  
208 have not been known to transmit rabies to humans in the United States. Bites from large rodents  
such as woodchucks (including groundhogs) and beavers, should be considered as possible rabies  
210 exposures, especially in regions where rabies is enzootic in raccoons (30). In all cases involving  
rodents, the state or local health department should be consulted before a decision is made to  
212 initiate antirabies postexposure prophylaxis (1).

214 Circumstances of Biting Incident

215 An UNPROVOKED attack is more likely than a provoked attack to indicate the animal is rabid.  
216 Bites inflicted on a person attempting to feed or handle an apparently healthy animal should  
217 generally be regarded as PROVOKED. A currently vaccinated dog, cat or ferret is unlikely to  
218 become infected with rabies (1).

219 Type of Exposure

220 Rabies is transmitted by introducing the virus into open cuts or wounds in skin or via mucous  
221 membranes. The likelihood of rabies infection varies with the nature and extent of exposure.

222 Two categories of exposure should be considered:

223 **Bite:** Any penetration of the skin by teeth. Bites to highly innervated areas such as the face and  
224 hands carry the highest risk, but the site of the bite should not influence the decision to begin  
225 treatment. Recent epidemiologic data suggest that even the very limited injury inflicted by a bat  
226 bite (compared to lesions caused by terrestrial carnivores) should prompt consideration of  
227 postexposure prophylaxis unless the bat is available for testing and is negative for evidence of  
228 rabies (1).

229 **Nonbite:** The contamination of open wounds, abrasions, mucous membranes, or theoretically,  
230 scratches, with saliva or other potentially infectious material (such as neural tissue) from a rabid  
231 animal constitutes a nonbite exposure. In all instances of potential human exposures involving  
232 bats, and the bat is not available for testing, postexposure prophylaxis might be appropriate even  
233 if a bite, scratch or mucous membrane exposure is not apparent when there is reasonable  
234 probability that such exposure might have occurred. Postexposure prophylaxis can be considered  
235 for persons who were in the same room as the bat and who might be unaware that a bite or direct  
236 contact had occurred (e.g., a sleeping person awakens to find a bat in the room or an adult  
237 witnesses a bat in the room with a previously unattended child, mentally disabled person, or  
238 intoxicated person) and rabies cannot be ruled out by testing the bat. Other contact by itself, such  
239 as petting a rabid animal and contact with blood, urine, or feces (e.g., guano) of a rabid animal,  
240 does not constitute an exposure and is not an indication for prophylaxis. Because the rabies virus  
241 is inactivated by desiccation and ultraviolet irradiation, in general, if the material containing the  
242 virus is dry, the virus can be considered noninfectious. Two cases of rabies have been attributed  
243 to probable aerosol exposures in laboratories, and two cases of rabies in Texas could possibly  
244 have been due to airborne exposures in caves containing millions of bats (1).

245 The only documented cases for rabies from human-to-human transmission occurred in eight  
246 patients, including two in the USA, who received corneas transplanted from persons who died of  
247 rabies undiagnosed at the time of death (1). Stringent guidelines for acceptance of donor corneas  
248 have been implemented to reduce this risk.

249 Bite and nonbite exposure from humans with rabies theoretically could transmit rabies, but no  
250 laboratory-diagnosed cases occurring under such situations have been documented. Each  
251 potential exposure to human rabies should be carefully evaluated to minimize unnecessary rabies  
252 prophylaxis (1).

253 Postexposure Treatment Schedule

(see also **Dosage and Administration** section below)

254 The essential components of rabies postexposure prophylaxis are prompt local treatment of  
255 wounds and administration of both Human Rabies Immune Globulin (HRIG) and vaccine.

256 A complete course of postexposure treatment for previously unvaccinated adults and children  
257 consists of a total of 5 doses of vaccine, each 1.0 mL: one IM injection (deltoid) on each of days  
258 0, 3, 7, 14 and 28. For previously immunized adults and children, a total of 2 doses of vaccine,  
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262 each 1.0 mL: one IM injection (deltoid) on each of days 0 and 3. No HRIG should be  
administered to previously vaccinated persons as it may blunt their rapid memory response to  
rabies antigen.

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### 1. Local Treatment of Wounds

266 Immediate and thorough washing of all bite wounds and scratches with soap and water is an  
important measure for preventing rabies. In animal studies, thorough local wound cleansing  
268 alone has been shown to reduce markedly the likelihood of rabies. Whenever possible, bite  
injuries should not be sutured to avoid further and/or deeper contamination. Tetanus prophylaxis  
270 and measures to control bacterial infection should be given as indicated (1).

### 2. Postexposure Prophylaxis of Rabies

272 The regimen for postexposure prophylaxis depends on whether or not the patient has been  
274 previously immunized against rabies (see below). For persons who have not previously been  
immunized against rabies, the schedule consists of an initial injection IM of HRIG exactly 20 IU  
276 per kilogram body weight in total. If anatomically feasible, the FULL DOSE of HRIG should be  
thoroughly infiltrated in the area around and into the wounds. Any remaining volume of HRIG  
278 should be injected IM at a site distant from rabies vaccine administration. HRIG should never be  
administered in the same syringe or in the same anatomical site as the rabies vaccine. HRIG is  
280 administered only once (for specific instructions for HRIG use, see the product package insert).  
The HRIG injection is followed by a series of 5 individual injections of RabAvert (1.0 mL each)  
282 given IM on days 0, 3, 7, 14 and 28. Postexposure rabies prophylaxis should begin the same day  
exposure occurred or as soon after exposure as possible. The combined use of HRIG and  
284 RabAvert is recommended by the CDC for both bite and non-bite exposures, regardless of the  
interval between exposure and initiation of treatment.

286 In the event that HRIG is not readily available for the initiation of treatment, it can be given  
through the seventh day after administration of the first dose of vaccine. HRIG is not indicated  
288 beyond the seventh day because an antibody response to RabAvert is presumed to have begun by  
that time (1).

290 The sooner treatment is begun after exposure, the better. However, there have been instances in  
which the decision to begin treatment was made as late as 6 months or longer after exposure due  
292 to delay in recognition that an exposure had occurred. Postexposure antirabies treatment should  
always include administration of both passive antibody (HRIG) and immunization, with the  
294 exception of persons who have previously received complete immunization regimens  
(preexposure or postexposure) with a cell culture vaccine, or persons who have been immunized  
296 with other types of vaccines and have had documented rabies antibody titers. Persons who have  
previously received rabies immunization should receive 2 IM doses of RabAvert: 1 on day 0 and  
298 another on day 3. They should not be given HRIG as this may blunt their rapid memory response  
to rabies antigen.

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### 3. Postexposure Prophylaxis Outside the United States

302 If postexposure treatment is begun outside the United States with regimens or biologics that are  
not used in the United States, it may be prudent to provide additional treatment when the patient  
304 reaches the USA. State or local health departments should be contacted for specific advice in  
such cases (1).

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## Contraindications

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In view of the almost invariably fatal outcome of rabies, there is no contraindication to  
310 postexposure prophylaxis, including pregnancy (1).

312 *Hypersensitivity*

314 History of anaphylaxis to the vaccine or any of the vaccine components constitutes a  
316 contraindication to preexposure vaccination with this vaccine.

318 In the case of postexposure prophylaxis, if an alternative product is not available, the patient  
320 should be vaccinated with caution with the necessary medical equipment and emergency supplies  
322 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 state health department or CDC.

**Warnings**

324 Anaphylaxis, encephalitis including death, meningitis, neuroparalytic events such as encephalitis,  
326 transient paralysis, Guillain-Barre Syndrome, myelitis, and retrobulbar neuritis; and multiple  
sclerosis have been reported to be temporally associated with the use of RabAvert. See  
328 **Precautions** and **Adverse Events** sections. A patient's risk of developing rabies must be carefully  
considered, however, before deciding to discontinue immunization.

330 RABAVERT MUST NOT BE USED SUBCUTANEOUSLY OR INTRADERMALLY.

332 RabAvert must be injected intramuscularly. For adults, the deltoid area is the preferred site of  
334 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 titers (1).

336 DO NOT INJECT INTRAVASCULARLY.

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

342 Development of active immunity after vaccination may be impaired in immune-compromised  
344 individuals. Please refer to **Drug Interactions**, under **Precautions**.

346 This product contains albumin, a derivative of human blood. It is present in RabAvert at  
348 concentrations of less than 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  
350 theoretical risk for transmission of Creutzfeld-Jakob disease (CJD) also is considered extremely  
remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

352

## Precautions

### 354 General

356 Care is to be taken by the health care provider for the safe and effective use of the product. The  
358 health care provider should also question the patient, parent or guardian about 1) the current  
360 health status of the vaccinee; and 2) reactions to a previous dose of RabAvert, or a similar  
362 product. Preexposure 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 should be used for each patient. 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.

### 364 Hypersensitivity

366 At present there is no evidence that persons are at increased risk if they have egg  
368 hypersensitivities that are not anaphylactic or anaphylactoid in nature. Although there is no safety  
370 data regarding the use of RabAvert in patients with egg allergies, experience with other vaccines  
372 derived from primary cultures of chick embryo fibroblasts demonstrates that documented egg  
374 hypersensitivity does not necessarily predict an increased likelihood of adverse reactions. There  
is no evidence to indicate that persons with allergies to chickens or feathers are at increased risk  
of reaction to vaccines produced in primary cultures of chick embryo fibroblasts.

372 Since reconstituted RabAvert contains processed bovine gelatin and trace amounts of chicken  
374 protein, neomycin, chlortetracycline and amphotericin B, the possibility of allergic reactions in  
individuals hypersensitive to these substances should be considered when administering the  
vaccine.

376 Epinephrine injection (1:1000) must be immediately available should anaphylactic or other  
allergic reactions occur.

378 When a person with a history of hypersensitivity must be given RabAvert, antihistamines may be  
380 given; epinephrine (1:1000), volume replacement, corticosteroids and oxygen should be readily  
available to counteract anaphylactic reactions.

### 382 Drug Interactions

384 Radiation therapy, antimalarials, corticosteroids, other immunosuppressive agents and  
386 immunosuppressive illnesses can interfere with the development of active immunity after  
388 vaccination, and may diminish the protective efficacy of the vaccine. Preexposure vaccination  
390 should be administered to such persons with the awareness that the immune response may be  
392 inadequate. Immunosuppressive agents should not be administered during postexposure therapy  
unless essential for the treatment of other conditions. When rabies postexposure 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 (1).

394 HRIG must not be administered at more than the recommended dose, since active immunization  
to the vaccine may be impaired.

396 No data are available regarding the concurrent administration of RabAvert with other vaccines.

### 398 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

#### 402 Use in Pregnancy

403 Pregnancy Category C. Animal reproductive studies have not been conducted with  
404 RabAvert. It is also not known whether RabAvert can cause fetal harm when  
405 administered to a pregnant woman or can affect reproduction capacity. RabAvert should  
406 be given to a pregnant woman only if clearly needed. The ACIP has issued recommendations  
407 for use of rabies vaccine in pregnant women (1).

#### 408 Use in Nursing Mothers

409 It is not known whether RabAvert is excreted in animal or human milk, but many drugs are  
410 excreted in human milk. Although there are no data, because of the potential consequences of  
411 inadequately treated rabies exposure, nursing is not considered a contraindication to postexposure  
412 prophylaxis. If the risk of exposure to rabies is substantial, preexposure vaccination might also  
413 be indicated during nursing.

#### 416 Pediatric Use

417 Children and infants receive the same dose of 1 mL, given IM, as do adults.

418 Only limited data on the safety and efficacy of RabAvert in the pediatric age group are available.  
419 However, in three studies some preexposure and postexposure experience has been gained (12,  
420 19, 26; see also **Clinical Studies in Clinical Pharmacology** section).

#### 422 Geriatric Use

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

### 428 **Adverse Reactions**

429 In very rare cases, neurological and neuromuscular events have been reported in temporal  
430 association with administration of RabAvert (see also **Warnings** section). These include cases of  
431 hypersensitivity (see **Contraindications, Warnings, and Precautions** sections).

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

435 A patient's risk of acquiring rabies must be carefully considered before deciding to discontinue  
436 vaccination. Advice and assistance on the management of serious adverse reactions for persons  
437 receiving rabies vaccines may be sought from the state health department or CDC (see also  
438 **Contraindications** section).

439 Local reactions such as induration, swelling and reddening have been reported more often than  
440 systemic reactions. In a comparative trial in normal volunteers, Dreesen *et al.* (4) described their  
441 experience with RabAvert compared to a HDCV rabies vaccine. Nineteen subjects received  
442 RabAvert and 20 received HDCV. The most commonly reported adverse reaction was pain at the  
443 injection site.

448 injection site, reported in 45% of the HDCV group, and 34% of the RabAvert group. Localized  
450 lymphadenopathy was reported in about 15% of each group. The most common systemic  
452 reactions were malaise (15 % RabAvert group vs. 25 % HDCV group), headache (10 % RabAvert  
454 group vs. 20 % HDCV group), and dizziness (15 % RabAvert group vs. 10 % HDCV group). In  
456 a recent study in the USA (5), 83 subjects received RabAvert and 82 received HDCV. Again, the  
458 most common adverse reaction was pain at the injection site in 80% in the HDCV group and 84%  
460 in the RabAvert group. The most common systemic reactions were headache (52% RabAvert  
462 group vs. 45% HDCV group), myalgia (53% RabAvert group vs. 38% HDCV group) and malaise  
(20% RabAvert group vs. 17% HDCV group). None of the adverse events were serious, almost  
all adverse events were of mild or moderate intensity. Statistically significant differences  
between vaccination groups were not found. Both vaccines were generally well tolerated.  
Uncommonly observed adverse events include temperatures above 38°C (100°F), swollen lymph  
nodes, pain in limbs and gastrointestinal complaints. In rare cases, patients have experienced  
severe headache, fatigue, circulatory reactions, sweating, chills, monoarthritis and allergic  
reactions; transient paresthesias and one case of suspected urticaria pigmentosa have also been  
reported.

#### 464 *Observed During Clinical Practice* (See **Warnings** and **Precautions**)

466 The following adverse reactions have been identified during post approval use of RabAvert.  
468 Because these reactions are reported voluntarily from a population of uncertain size, estimates of  
470 frequency cannot be made. These events have been chosen for inclusion due to their seriousness,  
frequency of reporting, causal connection to RabAvert, or a combination of these factors:

472 Allergic: Anaphylaxis, Type III hypersensitivity-like reactions, bronchospasm, urticaria, pruritis,  
edema

474 CNS: Neuroparalysis, encephalitis, meningitis, transient paralysis, Guillain-Barre Syndrome,  
myelitis, retrobulbar neuritis, multiple sclerosis, vertigo, visual disturbance

476 Cardiac: Palpitations, hot flush

Local: Extensive limb swelling

478 The use of corticosteroids to treat life-threatening neuroparalytic reactions may inhibit the  
development of immunity to rabies (see **Precautions**, *Drug Interactions*).

480 Once initiated, rabies prophylaxis should not be interrupted or discontinued because of local or  
482 mild systemic adverse reactions to rabies vaccine. Usually such reactions can be successfully  
managed with anti-inflammatory and antipyretic agents.

#### 484 *Reporting of Adverse Events*

486 Adverse events should be reported by the health care provider or patient to the US Department of  
488 Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS).  
Report forms and information about reporting requirements or completion of the form can be  
490 obtained from VAERS by calling the toll-free number 1-800-822-7967 (1). In the USA, such  
events can be reported to the Professional Services department, Novartis Vaccines and  
Diagnostics, Inc.: phone: 1-800-244-7668.

### 492 **Dosage and Administration**

494 The individual dose for adults, children, and infants is 1 mL, given intramuscularly.

496 In adults, administer vaccine by IM injection into the deltoid muscle. In small children and  
498 infants, administer vaccine into the anterolateral zone of the thigh. The gluteal area should be  
500 avoided for vaccine injections, since administration in this area may result in lower neutralizing  
antibody titers. 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.

502

### A. Preexposure Dosage

504

#### 1. Primary Immunization

506 In the United States, the Advisory Committee on Immunization Practices (ACIP) recommends  
three injections of 1.0 mL each: one injection on day 0 and one on day 7, and one either on day  
508 21 or 28 (for criteria for preexposure vaccination, see Table 1).

510

#### 2. Booster Immunization

The individual booster dose is 1 mL, given intramuscularly.

512

Booster immunization is given to persons who have received previous rabies immunization and  
remain at increased risk of rabies exposure by reasons of occupation or avocation.

514

Persons who work with live rabies virus in research laboratories or vaccine production facilities  
(continuous-risk category: see Table 1) should have a serum sample tested for rabies antibodies  
516 every 6 months. The minimum acceptable antibody level is complete virus neutralization at a 1:5  
serum dilution by the rapid fluorescent focus inhibition test (RFFIT). A booster dose should be  
518 administered if the titer falls below this level.

520

The frequent-risk category includes other laboratory workers such as those doing rabies  
diagnostic testing, spelunkers, veterinarians and staff, animal-control and wildlife officers in areas  
where rabies is epizootic. Persons in the frequent-risk category should have a serum sample  
522 tested for rabies antibodies every 2 years and, if the titer is less than complete neutralization at a  
1:5 serum dilution by RFFIT, should have a booster dose of vaccine. Alternatively, a booster can  
524 be administered in the absence of a titer determination.

526

The infrequent-risk category, including veterinarians, animal-control and wildlife officers  
working in areas of low rabies enzooticity (infrequent-exposure group) and international travelers  
to rabies enzootic areas do not require routine preexposure booster doses of RabAvert after  
528 completion of a full primary preexposure vaccination scheme (Table 1).

530

### B. Postexposure Dosage

**Immunization should begin as soon as possible after exposure.** A complete course of  
532 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 HRIG on day 0. For children, see

534

**Pediatric Use** section under **Precautions**.

Begin with the administration of HRIG. Give 20 IU/kg body weight.

536

This formula is applicable to all age groups, including infants and children. The recommended  
dosage of HRIG should not exceed 20 IU/kg body weight because it may otherwise interfere with  
538 active antibody production. Since vaccine-induced antibody appears within 1 week, HRIG is not  
indicated more than 7 days after initiating postexposure prophylaxis with RabAvert. If  
540 anatomically feasible, the FULL DOSE of HRIG should be thoroughly infiltrated in the area  
around and into the wounds. Any remaining volume of HRIG should be injected IM at a site  
542 distant from rabies vaccine administration. HRIG should never be administered in the same  
syringe or in the same anatomical site as the rabies vaccine.

544 Because the antibody response following the recommended immunization regimen with  
546 RabAvert has been satisfactory, routine post-immunization serologic testing is not recommended.  
548 Serologic testing is indicated in unusual circumstances, as when the patient is known to be  
immunosuppressed. Contact the appropriate state health department or the CDC for  
recommendations.

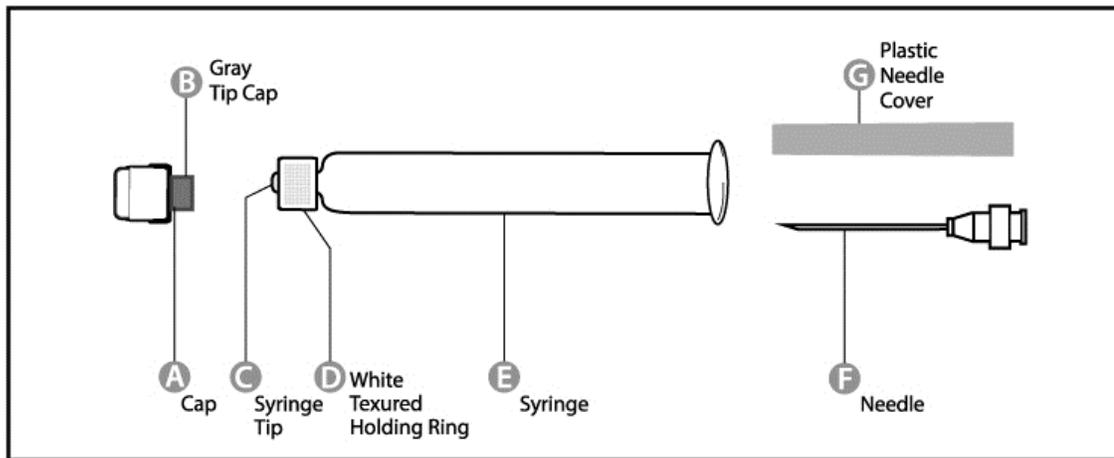
550 C. Postexposure Prophylaxis of Previously Immunized Persons

552 When rabies exposure occurs in a previously vaccinated person, then that person should receive  
554 two IM (deltoid) doses (1.0 mL each) of RabAvert: one immediately and one 3 days later. HRIG  
556 should not be given in these cases. Persons considered to have been immunized previously are  
558 those who received a complete preexposure vaccination or postexposure prophylaxis with  
560 RabAvert or other tissue culture vaccines or have been documented to have had a protective  
antibody response to another rabies vaccine. If the immune status of a previously vaccinated  
person is not known, full postexposure antirabies treatment (HRIG plus 5 doses of vaccine) is  
recommended. In such cases, if a protective titer can be demonstrated in a serum sample  
collected before vaccine is given, treatment can be discontinued after at least two doses of  
vaccine.

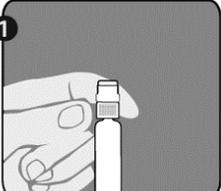
Instructions for Reconstituting RabAvert

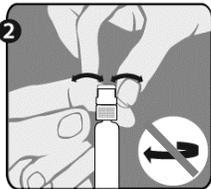
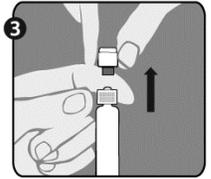
562 Parenteral drug products should be inspected visually for particulate matter and discoloration  
564 prior to administration. If either of these conditions exists, the vaccine should not be  
administered.

566



568

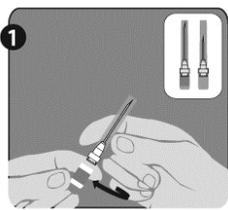
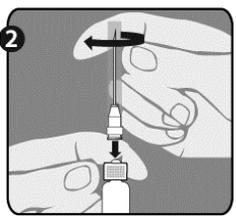
<p><b>Step 1:</b> With one hand, hold the syringe (E) with the cap pointing upward. Be sure to hold the syringe by the white textured holding ring (D).</p>	 <p>The illustration shows a hand holding the syringe by the white textured holding ring (D). A small circle with the number '1' is in the top left corner of the illustration, indicating the first step.</p>
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<p><b>Step 2:</b> With the other hand, grasp the cap (A) and firmly rock it back and forth to break its connection to the white textured holding ring (D). <b>Do not twist or turn the cap.</b></p>	
<p><b>Step 3:</b> Lift up to remove the cap (A) and the attached gray tip cap (B). Be careful not to touch the sterile syringe tip (C).</p>	

570

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

572

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

574

The package contains a vial of freeze-dried vaccine, a syringe containing 1 mL of sterile diluent, a sterile needle for reconstitution and a sterile needle suitable for intramuscular injection. The longer of the 2 needles supplied is the reconstitution needle. Affix the reconstitution needle 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, freeze-dried vaccine dissolves to give a clear or slightly opaque suspension. Withdraw the total amount of dissolved vaccine into the syringe and replace the long needle with the smaller needle for IM injection. The reconstituted vaccine should be used immediately. A separate, sterile syringe and needle should be used for each patient. Needles must not be recapped and should be properly disposed of. 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.

592



594

## How Supplied

596 RabAvert product presentation is listed in Table 3 below:

598 **TABLE 3: RABAVERT PRODUCT PRESENTATION**

Presentation	Carton NDC Number	Components
Single dose kit	63851-501-02	<ul style="list-style-type: none"> <li>• 1 vial of freeze-dried vaccine containing a single dose [NDC 63851-511-11]</li> <li>• 1 disposable pre-filled syringe of Sterile Diluent for reconstitution (1 mL) [NDC 63851-512-12]</li> <li>• 1 small needle for injection (25 gauge, 1 inch) and 1 long needle for reconstitution (21 gauge, 1 ½ inch)</li> </ul>

600

CAUTION: Federal law prohibits dispensing without a prescription.

602

## Storage

604

RabAvert should be stored protected from light at 2°C to 8°C (36°F to 46°F). After reconstitution the vaccine is to be used immediately. The vaccine may not be used after the expiration date given on package and container.

608

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