C H I R O N
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Rabies Vaccine
RabAvert™

Rabies Vaccine for Human Use

Description

RabAvert, rabies vaccine, produced by Chiron Behring GmbH & Co 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), 1 mg potassium glutamate and 0.3 mg sodium EDTA. Small quantities of bovine serum are used in the cell culture process. Testing of the product components and excipients using currently available methods has not detected any adventitious agents. Further, bovine components originate only from source countries known to be free of bovine spongioform encephalopathy. 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 mcg, chlortetracycline at < 20 ng, and amphotericin B at < 2 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 diluent (Water For Injection, USP). 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 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 outbreaks 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 post-exposure prophylaxis.

Rabies is almost invariably fatal due to encephalomyelitis. Modern day prophylaxis has proven nearly 100% successful; most human fatalities now occur in people who fail to seek medical treatment, usually because they do not recognize a risk in the animal contact leading to the infection. Inappropriate post-exposure prophylaxis may also result in clinical rabies. Survival after clinical rabies is extremely rare, and is associated with severe brain damage and permanent disability.

RabAvert (in combination with passive immunization with Human Rabies Immune Globulin (HRIG) and local wound treatment) in post-exposure immunization against rabies has been shown to protect, patients of all age groups from rabies, when the vaccine was administered according to the World Health Organization (WHO) guidelines and as soon as possible after rabid animal contact. Anti-rabies antibody titers after immunization have been shown to reach levels well above the minimal protective level of 0.5 IU/mL within 14 days after initiating the immunization series. The minimal antibody titer accepted as seroconversion is 0.5 IU, measured by the rapid fluorescent inhibition test (RFFIT) as

specified by the WHO (1, 2) or a 1:5 titer (complete inhibition in RFFIT at 1:5 dilution) as specified by the CDC. Vaccine failure has only been reported when key elements of rabies post-exposure regimens were omitted or when the vaccine has been incorrectly administered.

Pre-exposure Immunization

The immunogenicity of RabAvert has been demonstrated in clinical trials conducted in different countries such as the USA (3, 4), UK (5), Croatia (6), and Thailand (7, 8, 9). When administered according to the recommended immunization schedule (days 0, 7, 21), 100% of subjects attained a protective titer. 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.

The ability of RabAvert to boost previously immunized subjects was evaluated in three clinical trials. In the Thailand study, pre-exposure booster doses were administered to 10 individuals. Antibody titers of > 0.5 IU/mL were present at baseline on day 0 in all subjects (8). 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 (10). In a trial carried out in the USA (3), 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.
Persistence of antibody after immunization with RabAvert has been evaluated. In a trial performed in the UK, neutralizing antibody titers > 0.5 IU/mL were present 2 years after immunization in all sera (6/6) tested.

Post-exposure Immunization

RabAvert, when used in the recommended post-exposure WHO program of 5 to 6 IM injections of 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 (7, 8, 11-14) within 14 days and in 215/216 patients by day 28 - 38.
Of these, 203 were followed for at least 10 months. No case of rabies was observed (7, 8, 11-18). Some patients received HRIG, 20 - 30 IU per kg body weight, or Equine Rabies Immune Globulin (ERIG), 40 IU per kg body weight, at the time of the first dose. In most studies (7, 8, 11, 15), the addition of either HRIG or ERIG caused a slight decrease in GMTs which was neither clinically relevant nor statistically significant. In one study (14), 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.
The results of several studies of normal volunteers who have been given the WHO regimen of vaccine for post-exposure use (10, 19-22), i.e., "simulated" post-exposure use, show that with sampling by day 28 - 30, 205/208 vaccinees had protective titers > 0.5 IU/mL.
Over a 10 year (7/85 - 6/95) period, 46 reports of suspected post-exposure vaccine failure have been evaluated (11.8 million doses distributed). In each case, post-exposure treatment had not been in compliance with WHO recommendations.

Indications and Usage

RabAvert is indicated for pre-exposure immunization, in both primary series and booster dose, and for post-exposure prophylaxis against rabies.
There are no data on the interchangeable use of different rabies vaccines in a single pre- or post-exposure series. Therefore the vaccine from a single manufacturer should be used for the complete series whenever possible. If vaccines from other manufacturers are administered during the immunization series, an adequate antibody response should be confirmed by appropriate serologic tests. However, for booster immunization, RabAvert was shown to elicit satisfactory antibody level responses in 41 persons who received a primary series with HDCV (3, 10).

A. Pre-exposure Immunization - See Table 1

Pre-exposure Immunization Schedule
Pre-exposure immunization consists of three doses of RabAvert 1.0 mL, intramuscularly (deltoid region), one each on days 0, 7, and 21 or 28 ([23] see also Table 1 for criteria for pre-exposure immunization).

Pre-exposure immunization should be offered to persons in high-risk groups, such as veterinarians, animal handlers, wildlife officers, 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 pre-exposure prophylaxis.

Pre-exposure immunization is given for several reasons. First, it may provide protection to persons with inapparent exposure to rabies. Second, it may protect persons whose post-exposure 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.
In some instances, pre-exposure immunization should be boosted periodically in an effort to provide continuous protection (see Table 1); each booster immunization consists of a single dose. See **Clinical Pharmacology**. Serum antibody determinations before and after booster immunization may be helpful in determining both the need for a booster dose and the timing of such a dose.

Table 1: Criteria for Pre-exposure Immunization

Risk Category and Nature of Risk	**Typical Populations**	**Pre-exposure regimen**
Continuous. Virus present continuously, often in high concentrations. Aerosol, mucous membrane, bite, or nonbite exposures may go unrecognized.	Rabies research lab workers,* rabies biologics production workers.	Primary course. Serologic testing every 6 months; booster vaccination when antibody level falls below acceptable level.*
Frequent. Exposure usually episodic, with source recognized, but exposure may also be unrecognized. Aerosol, mucous membrane, bite or nonbite exposure.	Rabies diagnostic lab workers,* spelunkers, veterinarians and staff, and animal-control and wildlife workers in rabies enzootic areas. Travelers visiting foreign areas of enzootic rabies for more than 30 days.	Primary course. Booster vaccination or serologic testing every 2 years.**
Infrequent (greater than population-at-large). Exposure nearly always episodic with source recognized. Mucous membrane, bite, or nonbite exposure.	Veterinarians and animal-control and wildlife workers in areas of low rabies enzooticity. Veterinary students.	Primary course. No routine booster vaccination or serologic testing.**
Rare (population-at-large). Exposures always episodic. Mucous membrane, or bite with source unrecognized.	US population-at-large, including individuals in rabies epizootic areas.	No vaccination necessary.

Adapted from the recommendations of the Immunization Practices Advisory Committee (ACIP) on rabies prevention.
MMWR, 1991; 40 (Suppl. RR-3): 1-19.

* Judgment of relative risk and extra monitoring of vaccination status of laboratory workers is the responsibility of the laboratory supervisor (see US Department of Health and Human Service's Biosafety in Microbiological and Biomedical Laboratories, 1984).

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

B. Post-exposure Immunization - See Table 2

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 (23).

Table 2: Rabies Post-exposure Prophylaxis Guide (Advisory Committee on Immunization Practices [ACIP]) (23)

Animal type	Evaluation and disposition of animal	Post-exposure prophylaxis recommendations
Dogs and cats	Healthy and available for 10 days observation	Should not begin prophylaxis unless animal develops symptoms of rabies*
	Rabid or suspected rabid	Immediate immunization
	Unknown (escaped)	Consult public health officials
Skunks, raccoons, bats, foxes, and most other carnivores; woodchucks	Regarded as rabid unless geographic area is known to be free of rabies or until animal proven negative by laboratory tests**	Immediate immunization
Livestock, rodents, and lagomorphs (rabbits and hares)	Consider individually	Consult public health officials. Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other rodents, rabbits, and hares almost never require antirabies treatment

* During the 10-day holding period, begin treatment with HRIG and RabAvert rabies vaccine at first sign of rabies in a dog or cat that has bitten someone. The symptomatic animal should be killed immediately and tested.

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

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

Species of Biting Animal

Carnivorous wild animals (especially skunks, raccoons, foxes and coyotes) and bats are the animals most commonly infected with rabies and have caused most of the indigenous cases of human rabies in the United States since 1960. Unless an animal is tested and shown not to be rabid, post-exposure prophylaxis should be initiated upon bite or nonbite exposure to the animals. (See 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, treatment can be discontinued (23).

The likelihood that a domestic dog or cat is infected with rabies varies from region to region; hence the need for post-exposure prophylaxis also varies (23).

Rodents (such as squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, and mice) and lagomorphs (including rabbits and hares) are rarely found to be infected with rabies and have not been known to cause human rabies in the United States. In these cases, the state or local health department should be consulted before a decision is made to initiate post-exposure antirabies prophylaxis (23).

Circumstances of Biting Incident

An UNPROVOKED attack is more likely than a provoked attack to indicate the animal is rabid. Bites inflicted on a person attempting to feed or handle an apparently healthy animal should generally be regarded as PROVOKED.

Type of Exposure

Rabies is transmitted by introducing the virus into open cuts or wounds in skin or via mucous membranes. The likelihood of rabies infection varies with the nature and extent of exposure. Two categories of exposure should be considered:

Bite: Any penetration of the skin by teeth. Bites to the face and hands carry the highest risk, but the site of the bite should not influence the decision to begin treatment (23).

Nonbite: Scratches, abrasions, open wounds, or mucous membranes contaminated with saliva or other potentially infectious material, such as brain tissue, from a rabid animal. Casual contact, such as petting a rabid animal (without a bite or nonbite exposure as described above), does not constitute an exposure and is not an indication for prophylaxis. There have been two instances of airborne rabies acquired in laboratories and two probable airborne rabies cases acquired in a bat-infested cave in Texas (23).

The only documented cases for rabies from human-to-human transmission occurred in four patients in the United States and overseas who received corneas transplanted from persons who died of rabies undiagnosed at the time of death (2). Stringent guidelines for acceptance of donor corneas should reduce this risk.

Bite and nonbite exposure from humans with rabies theoretically could transmit rabies, although no cases of rabies acquired this way have been documented. Each potential exposure to human rabies should be carefully evaluated to minimize unnecessary rabies prophylaxis (23).

Post-exposure Immunization Schedule

The essential components of rabies post-exposure prophylaxis are prompt local treatment of wounds and immunization, including administration, in most instances of both globulin and vaccine (Table 2).

A complete course of post-exposure immunization for previously unvaccinated adults and children consists of a total of 5 doses, each 1.0 mL: one IM injection on each of days 0, 3, 7, 14 and 28.

1. Local Treatment of Wounds

Immediate and thorough washing of all bite wounds and scratches with soap and water is an important measure for preventing rabies. In animal studies, simple local wound cleansing 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 and measures to control bacterial infection should be given as indicated (23).

2. Specific Treatment of Rabies

The injection schedule for post-exposure prophylaxis depends on whether the patient has had or has not had previous immunization against rabies. For persons who have not previously been immunized against rabies, the schedule consists of an initial injection IM of HRIG exactly 20 IU per kilogram body weight in total. If anatomically feasible, up to half of the dose of HRIG should be thoroughly infiltrated in and around the wound(s) and the remainder should be administered IM in the gluteal region. HRIG is 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) given IM on days 0, 3, 7, 14 and 28. Administration of HRIG and RabAvert should be given at separate sites using separate syringes. Post-exposure rabies prophylaxis should begin the same day exposure occurred or as soon after exposure as possible. The combined use of HRIG and RabAvert is recommended for both bite and non-bite exposures, regardless of the interval between exposure and initiation of treatment.

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 beyond the seventh day because an antibody response to RabAvert is presumed to have begun by that time (23).

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 to delay in recognition that an exposure had occurred. Post-exposure antirabies immunization should always include administration of both passive antibody and immunization with the exception of persons who have previously received complete immunization regimens (pre-exposure or post-exposure) with a cell culture vaccine, or persons who have been immunized 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 another on day 3. They should not be given HRIG.

3. Treatment Outside the United States

If post-exposure immunization is begun outside the United States with regimens or products that are not used in the United States, it may be desirable to provide additional treatment when the patient reaches the USA. State or local health departments should be contacted for specific advice in such cases (23).

Contraindications

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

However, if an alternative product (e.g. HDCV or Rabies Vaccine Adsorbed [RVA]) is not available, care should be taken if the vaccine is to be administered to persons known to be sensitive to processed bovine gelatin, chicken protein, neomycin, chlortetracycline and amphotericin B in trace amounts, which may be present in the vaccine and may cause an allergic reaction in such individuals.

Warnings

Serious systemic anaphylactic reactions have been reported and neuroparalytic events have been reported in temporal association with RabAvert, rabies vaccine, administration. Against the background of 11.8 million doses distributed worldwide as of June 30, 1995, 10 cases of encephalitis (1 death) or meningitis, 7 cases of transient paralysis (including 2 cases of Guillain-Barré Syndrome), 1 case of myelitis, 1 case of retrobulbar neuritis, and 2 cases of suspected multiple sclerosis have been temporally associated with the use of RabAvert. Also 2 cases of anaphylactic shock have been reported. Such events pose a dilemma for the attending physician. A patient's risk of developing rabies must be carefully considered, however, before deciding to discontinue immunization.

RABAVERT MUST NOT BE USED SUBCUTANEOUSLY OR INTRADERMALLY!
RabAvert must be injected intramuscularly. For adults, the deltoid area is the preferred site of immunization; for small children, 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 (2).

DO NOT INJECT INTRAVASCULARLY!
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***, under **Precautions**.

Precautions

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 or a sterile disposable unit should be used for each patient to prevent transmission of hepatitis and other infectious agents from person to person. Needles should not be recapped and should be properly disposed of. As with any vaccine, vaccination with RabAvert may not protect 100% of susceptible individuals.

Hypersensitivity

RabAvert is produced in chick embryo cell culture. Persons with a history of anaphylactic, anaphylactoid, or other immediate reactions (e.g. hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion should not be immunized with this vaccine. At present there is no evidence that persons are at increased risk if they have egg hypersensitivities that are not anaphylactic or anaphylactoid in nature; however, in this case, HDCV rabies vaccines or RVA should be administered. There is no evidence to indicate that persons with allergies to chickens or feathers are at increased risk of reaction to vaccines produced in chick embryo cell culture.

Since reconstituted RabAvert contains traces of processed bovine gelatin, chicken protein, neomycin, chlortetracycline and amphotericin B, the possibility of allergic reactions in individuals sensitive to these substances should be considered when administering the vaccine.
Epinephrine injection (1:1000) must be immediately available should anaphylactic or other allergic reactions occur.
When a person with a history of hypersensitivity must be given RabAvert, antihistamines may be given; epinephrine (1:1000), volume replacement, corticosteroids and oxygen should be readily available to counteract anaphylactic reactions.

Drug Interactions

Corticosteroids, other immunosuppressive agents, antimalarials and immunosuppressive illnesses can interfere with the development of active immunity after vaccination, and may diminish the protective efficacy of the vaccine. Pre-exposure prophylaxis should be administered to such persons with the awareness that the immune response may be inadequate. Immunosuppressive agents should not be administered during post-exposure therapy 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 be tested for rabies antibody to ensure that an acceptable antibody response has been induced (23).

Rabies Immuno Globulin must not be administered at more than the recommended dose, since response to active immunization may be impaired.

Use in Pregnancy

Category C. 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. RabAvert should be given to a pregnant woman only if clearly needed. However, because of the potential consequences of inadequately treated rabies exposure, and limited data which indicate that fetal abnormalities have not been associated with rabies vaccination, pregnancy is not considered a contraindication to post-exposure prophylaxis. If there is substantial risk of exposure to rabies, pre-exposure prophylaxis may also be indicated during pregnancy. However, in such instances, consideration should be given to removing the pregnant woman from the high risk environment.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Adverse Reactions

SEE ALSO **WARNINGS** AND **CONTRAINDICATIONS** SECTIONS FOR ADDITIONAL STATEMENTS

Local reactions such as induration, swelling and reddening have been reported more often than systemic reactions. In a comparative trial in normal volunteers, Dreesen ***et al.*** (3, 24) described their experience with RabAvert compared to a HDCV rabies vaccine. Nineteen subjects received RabAvert and 20 received HDCV. The most commonly reported adverse reaction was pain at the injection site, reported in 45% of the HDCV group, and 34% of the RabAvert group. Localized lymphadenopathy was reported in about 15% of each group. The most common systemic reactions were malaise (15 % RabAvert group vs. 25 % HDCV group), headache (10 % RabAvert group vs. 20 % HDCV group), and dizziness (15 % RabAvert group vs. 10 % HDCV group). In a recent study in the USA (4), 83 subjects received RabAvert and 82 received HDCV. Again, the most common adverse reaction was pain at the injection site in 80% in the HDCV group and 84% in the RabAvert group. The most common systemic reactions were headache (52% RabAvert 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 was 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, 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.

Type III hypersensitivity reactions in pre-exposure booster immunizations have been reported with one HDCV rabies vaccine (25 - 27). These reactions are thought to be due to small amounts of human serum albumin (HSA) rendered allergenic by beta-propiolactone (23, 28, 29). Human serum albumin (HSA) is present in RabAvert at concentrations less than 0.3 µg/dose. No type III hypersensitivity reactions have been observed with RabAvert (30).

Serious systemic anaphylactic reactions or neuroparalytic events have been reported in association with RabAvert administration. Against a background of 11.8 million doses distributed world-wide 10 cases of encephalitis (1 death) or meningitis, 7 cases of transient paralysis including 2 cases of Guillain-Barré Syndrome, 1 case of myelitis, 1 case of retrobulbar neuritis, and 2 cases of suspected multiple sclerosis have been temporally associated with the use of RabAvert. Also, 2 cases of anaphylactic shock have been reported. A patient's risk of developing rabies must be carefully considered, however, before deciding to discontinue immunization (see **Warnings**).

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

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.

Reporting of Adverse Events

Adverse events should be reported by the health care provider or patient to the US Department of 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 obtained from VAERS by calling the toll-free number 1-800-822-7967 (26). In the USA, such events can be reported to the Professional Services Department, Chiron Corporation: phone: 1-888-CHIRON-7.

Dosage and Administration

The individual dose is 1 mL, given intramuscularly.
Administer in adults by IM injection into the deltoid muscle or, in the case of small children, 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 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.

Instructions for Reconstituting RabAvert

Using the longer of the 2 needles supplied, transfer the entire contents of the diluent vial 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.
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. A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of hepatitis and other infectious agents from person to person. Needles should not be recapped and should be properly disposed of.
No data are available regarding the concurrent administration of RabAvert rabies vaccine with other vaccines.

Pediatric Use

Children and adults receive the same dose of 1 mL, given IM.
Only limited data on the safety and efficacy of RabAvert in the pediatric age group are available. However, in four studies some pre-exposure and post-exposure experience has been gained (17, 31, 32, 33).

Pre-exposure:
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 (32). In another study in Mexico, 15/21 children aged 7 - 18 years had antibody titers of ≥ 0.5 IU/mL on day 14, and all 21 children had antibody titers of ≥ 0.5 IU/mL on day 30. Only mild local pain was noted in approximately one quarter of the children (33).

Post-exposure:
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 (17). 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 (31).

A. Pre-exposure Dosage

1. Primary Immunization
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 21 or 28 (for criteria for pre-exposure immunization, see Table 1).

2. Booster Immunization
The individual booster dose is 1 mL, given intramuscularly.
Booster immunization is given to persons who have received previous rabies immunization and remain at increased risk of rabies exposure by reasons of occupation.
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 every 6 months. Booster doses of vaccine should be given to maintain a serum titer > 1 : 5 serum dilution by the RFFIT.
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, and international travelers living or visiting (for > 30 days) in areas where canine rabies is endemic. Persons among this group should have a serum sample 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 be administered in the absence of a titer determination.
Veterinarians and animal-control and wildlife officers working in areas of low rabies enzooticity (infrequent-exposure group) do not require routine pre-exposure booster doses of RabAvert after completion of a full primary pre-exposure immunization scheme (Table 1).

B. Post-exposure Dosage

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 HRIG on day 0. For children, see ***Pediatric Use*** section, above.
Begin with the administration of HRIG. Give 20 IU/kg body weight.
This formula is applicable to all age groups, including children. The recommended dosage of HRIG should not exceed 20 IU/kg body weight because it may otherwise interfere with active antibody production. Since vaccine-induced antibody appears within 1 week, HRIG is not indicated more than 7 days after initiating post-exposure immunization with RabAvert. If possible, up to one-half the dose of HRIG should be thoroughly infiltrated in the area around the wound and the rest should be administered IM, in a different site from the rabies vaccine, preferably in the gluteal area.
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. Contact state health department or CDC for recommendations.

C. Post-exposure Therapy of Previously Immunized Persons

When rabies exposure occurs in an immunized person who was vaccinated according to the recommended regimen with RabAvert or other tissue culture vaccines or who had previously demonstrated rabies antibody, that person should receive two IM doses (1.0 mL each) of RabAvert: one immediately and one 3 days later. HRIG should not be given in these cases. Persons should be considered to have been immunized previously if they received pre- or post-exposure prophylaxis with RabAvert or other tissue culture vaccines or have been documented to have had an adequate antibody response to duck embryo rabies vaccine. If the immune status of a previously vaccinated person is not known, full primary post-exposure antirabies treatment (HRIG plus 5 doses of vaccine) may be necessary. In such cases, if antibodies can be demonstrated in a serum sample collected before vaccine is given, treatment can be discontinued after at least two doses of vaccine.

How Supplied

Package with:
1 vial of freeze-dried vaccine containing a single dose
1 vial of sterile Water For Injection, USP (1 mL)
1 disposable syringe
1 smaller needle for injection, 25 gauge × 1 "
1 longer needle for reconstitution, 21 gauge ×1.5 "

N.D.C.# 53905-501-01
CAUTION: Federal law prohibits dispensing without a prescription

Storage

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.

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