PRODUCT MONOGRAPH

IMOVAX® Rabies

Rabies Vaccine Inactivated (DCO)

1 Dose = ≥2.5 IU Rabies Antigen

Powder and Diluent for Suspension for Injection

ATC Code: J07BG01 Rabies, inactivated, whole virus

Active Immunizing Agent
(For the Prevention of Rabies)

Manufactured by:
Sanofi Pasteur SA
Lyon, France

Distributed by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

Submission Control Number: 102730 **Date of Approval: 09 March 2006**

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Rabies Vaccine Inactivated (DCO)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1: Product Information

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients (per 1 mL)
Intramuscular injection	Powder and Diluent for Suspension for Injection Each 1 mL dose is formulated to contain: ≥2.5 IU Rabies virus (WISTAR Rabies PM/WI 38 1503-3M Strain)	Human albumin Neomycin **Diluent** Sterile water for injection

DESCRIPTION

IMOVAX® Rabies [Rabies Vaccine Inactivated (DCO)] produced by Sanofi Pasteur SA is a sterile, stable, freeze-dried suspension of rabies virus prepared from WISTAR Rabies PM/WI 38 1503-3M strain. The virus is harvested from infected MRC-5 human diploid cells, concentrated by ultrafiltration and inactivated by beta-propiolactone. The vaccine contains no preservative.

INDICATIONS AND CLINICAL USE

IMOVAX® Rabies [Rabies Vaccine Inactivated (DCO)] is indicated for the active immunization of individuals of all age groups to prevent disease caused by the rabies virus. It is indicated for both pre-exposure immunization (both primary series and booster doses) and post-exposure immunization.

Pre-Exposure Immunization

Primary Immunization

Pre-exposure rabies immunization is an elective procedure and should be offered to persons at potentially high 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. (1)

Pre-exposure immunization should be considered for travellers intending to live or work in areas where rabies is enzootic and where rabies control programs for domestic animals are inadequate, or where adequate and safe post-exposure facilities are unavailable. This includes: persons with frequent risk of rabies exposure; (1) children in rabies enzootic areas who are too young to understand the need to avoid animals or to report an animal bite; (1) persons in rabies enzootic areas where there is limited access to tissue culture vaccines and/or immune globulin or where ready transportation to an appropriate health-care facility cannot be assured. (2) (3)

Pre-exposure vaccination does not eliminate the need for prompt prophylaxis following an exposure but it eliminates the need for Rabies Immune Globulin (RIG) except in immunocompromised persons. (4) Any exposed person should receive appropriate wound treatment (see Management of Persons After Possible Exposure to Rabies) and a vaccine post-exposure treatment regimen. (5) (See DOSAGE, Dosing Considerations.)

Booster Doses

Persons with continuing high risk of exposure such as veterinarians, should have their serum tested for rabies antibodies every 2 years; others working with live rabies virus in laboratories or vaccine-production facilities and who are at risk of inapparent exposure should be tested every 6 months. (4) Those with inadequate titres should be given a booster dose of IMOVAX® Rabies. Persons previously immunized with other vaccines should be given sufficient doses of IMOVAX® Rabies to produce an adequate antibody response. The Canadian national rabies reference laboratory considers an acceptable antibody response to be a titre of $\geq$0.5 IU/mL by the Rapid Fluorescent-Focus Inhibition Test (RFFIT). (1)

Post-Exposure Management

Because it is not possible to determine which exposed individuals will develop rabies if untreated and because the infection is almost always fatal, it is essential that everyone exposed to animals with proven or suspected rabies be given post-exposure prophylaxis. The essential components of rabies post-exposure prophylaxis are local treatment of wounds and vaccination, and, in most cases RIG. (1) (4) (5)

A decision on the management of a person who may have been exposed to the rabies virus must be made rapidly and judiciously since delays in starting a post-exposure prophylaxis reduce its effectiveness, and the disease, once established, is almost always fatal. (1) Post-exposure prophylaxis should be started as soon as possible after exposure and should be offered to exposed individuals regardless of the elapsed interval. When notification of an exposure is delayed, prophylaxis may be started as late as 6 or more months after exposure. (1)

Rabies prophylaxis must be considered in every incident where potential exposure to rabies virus has occurred. In evaluating each case, local public health officials should be consulted. For further information on the factors to be considered in evaluating exposure consult the current edition of the Canadian Immunization Guide.

***Bite*:** any penetration of the 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 persons are sleeping unattended in a room where a bat is found or when the possibility of a bite cannot be reasonably excluded post-exposure prophylaxis should be initiated. (1)

***Non-bite*:** including contamination of scratches, abrasions or cuts of the skin or mucous membranes by saliva or other potentially infectious material, such as the brain tissue of a rabid animal. 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. (1)

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. (1)

Management of Persons After Possible Exposure to Rabies

Table 2 outlines the recommendations for the management of persons 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. (1)

Immediate washing and flushing with soap and water and a virucidal agent is imperative and is probably the most effective procedure in the prevention of rabies. Suturing the wound should be avoided if possible. Tetanus prophylaxis and antibacterial drugs should be given as required. (1)

Table 2: Post-exposure Prophylaxis for Persons Not Previously Immunized Against Rabies (1)

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 treatment of wound 2. At first sign of rabies in animal, give RIG (local +/- intramuscular) and start IMOVAX® Rabies
	Rabid or suspected to be rabid Unknown or escaped	1. Local treatment of wound 2. RIG (local +/- intramuscular) and IMOVAX® Rabies
Skunk, bat, fox, coyote, raccoon and other carnivores. Includes bat found in room when a person was sleeping unattended.	Regard as rabid unless geographic area is known to be rabies-free	1. Local treatment of wound 2. RIG (local +/- intramuscular) and IMOVAX® Rabies
Livestock, rodents or lagomorphs (hares and rabbits)	Consider individually. Consult appropriate public health and food inspection or agricultural officials. Bites of squirrels, chipmunks, rats, mice, hamsters, gerbils, other rodents, rabbits and hares may warrant post-exposure rabies prophylaxis if the behaviour of the biting animal was highly unusual.	
RIG = (human) rabies immune globulin		

The course of vaccine may be discontinued after consultation with pubic health/infectious disease experts if the direct fluorescent antibody test of the brain of an animal killed at the time of attack proves to be negative. However, if suspicion of rabies in the animal remains high even in the presence of a negative test, the immunization series should be continued.

Geriatrics

Evidence from experience suggests that rabies vaccine is efficacious in the geriatric population. (6)

Pediatrics

Safety and effectiveness in children have been established. (7) The indications for infants and children are the same as for adults.

CONTRAINDICATIONS

There are no definite contraindications to the use of IMOVAX® Rabies [Rabies Vaccine Inactivated (DCO)] in the post-exposure situation; however, care should be taken if the vaccine is to be administered to persons who are hypersensitive to rabies vaccine or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph. Local public health should be consulted if questions arise about the need for post-exposure treatment and expert opinion should be sought in the management of these individuals. (1)

Pre-exposure prophylaxis should not be administered to persons who are hypersensitive to this vaccine or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph. Persons who are at high-risk of contracting rabies disease and who have a hypersensitivity to the vaccine or one of its components may be referred for an evaluation by an allergist.

WARNINGS AND PRECAUTIONS

General

As with any vaccine, immunization with IMOVAX® Rabies [Rabies Vaccine Inactivated (DCO)] may not protect 100% of individuals.

Pre-exposure immunization with IMOVAX® Rabies should be deferred in the presence of any acute illness, including febrile illness.

Local and/or mild systemic reactions may occur after vaccine injection but these are usually transient and do not contraindicate continuing immunization.

Interchanging IMOVAX® Rabies with other rabies vaccines during a pre- or post-exposure series is not recommended because of a lack of data on the safety and efficacy of such a regimen. The immunization series should, whenever possible, be completed with the same product. When this is not feasible, the series may be completed with another WHO-approved cell-culture vaccine. (8) (9)

Although no post-exposure vaccine failures have occurred in Canada or the US since cell culture vaccines have been routinely used, failures have occurred abroad when some deviation was made from the recommended post-exposure treatment protocol or when less than the currently recommended amount of antirabies sera was administered. Specifically, subjects who contracted rabies after post-exposure prophylaxis did not have their wounds cleansed with soap and water, did not receive their rabies vaccine injections in the deltoid area (i.e., vaccine was administered in the gluteal area), or where the wound site was not properly infiltrated with RIG. (1) (5) (See Dosage and Administration section.)

This is a single dose of vaccine. In both pre-exposure and post-exposure immunization, the full 1.0 mL dose should be given intramuscularly. (See Dosage and Administration section.)

In adults and children the vaccine should be injected into the deltoid muscle. In infants and small children the mid-lateral aspect of the thigh may be preferable. There have been reports of possible vaccine failure when the vaccine has been administered in the gluteal area. (10) (11)

This vaccine must not be used subcutaneously or intradermally. Special care should be taken to ensure that the product is not injected into a blood vessel.

A separate, sterile syringe and needle, or a sterile disposable unit, must be used for each individual patient to prevent the transmission of infectious agents. There have been case

reports of transmission of HIV and hepatitis by failure to scrupulously observe sterile technique.

Before administration of IMOVAX® Rabies, take all appropriate precautions to prevent adverse reactions. This includes a review of the patient's history concerning possible hypersensitivity to the vaccine or similar vaccine, previous immunization history, the presence of any contraindications to immunization and current health status. The health-care provider should inform the patient, parent or guardian of the benefits and risks of immunization, inquire about the recent health status of the patient and comply with any local requirements with respect to information to be provided to the patient before immunization and the importance of completing the immunization series.

This product contains albumin, a derivative of human blood. 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 Creutzfeldt-Jakob disease (vCJD) is also considered extremely remote. No cases of transmission of viral diseases or vCJD have ever been attributed to albumin.

Hematologic

Intramuscular injections should be given with care in persons with coagulation disorders or on anticoagulant therapy because intramuscular injection can cause injection site hematoma. (1)

Immune

As with other products, Epinephrine Hydrochloride Solution (1:1000) and other appropriate agents should be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs. (1) Health-care providers should be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings, including proper airway management. (12) (13) For instructions on recognition and treatment of anaphylactic reactions, see the current edition of the Canadian Immunization Guide or visit the Health Canada website.

The possibility of allergic reactions in individuals sensitive to components of the vaccine should be evaluated.

Since the vaccine contains traces of neomycin and phenol red, the possibility of allergic reactions in individuals sensitive to these substances should be borne in mind.

Corticosteroids, immunosuppressive agents, and immunosuppressive illnesses can interfere with the development of active immunity after vaccination. 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 steroids 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 developed. (5) For immunodeficient individuals, this test can be performed 2 to 4 weeks after the vaccination. Pre-exposure prophylaxis should be administered to such persons with the awareness that the immune response may be inadequate. Antibody titre determination is also advisable after pre-exposure immunization in these populations. (5) (9)

Failures to seroconvert after the third dose should be managed in consultation with appropriate public health officials.

In the case of pre-exposure immunization, a significant increase has been noted in "immune complex-like" reactions in persons receiving booster doses of IMOVAX® Rabies. (See Adverse Reactions.)

Special Populations

Pregnant Women:

The safety of rabies vaccines in pregnancy has not been established. IMOVAX® Rabies has not been studied in animal teratogenicity studies. It is also not known whether IMOVAX® Rabies can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. IMOVAX® Rabies should be given to a pregnant woman only if clearly needed.

Pre-exposure

In the absence of sufficient human data, postponement of pre-exposure vaccination is recommended. If there is a substantial risk of exposure to rabies, pre-exposure prophylaxis may be indicated during pregnancy. (5) (8)

Post-exposure

Because of the potential consequences of inadequately treated rabies exposure, and because there is no indication that fetal abnormalities have been associated with rabies vaccination, pregnancy is not considered a contraindication to postexposure prophylaxis. (5)

Nursing Women:

It is not known whether this vaccine is excreted in human milk. Caution must be exercised when pre-exposure vaccine is administered to a nursing mother. The US Advisory Committee on Immunization Practices (ACIP) states that inactivated vaccines administered to a lactating woman do not affect the safety of breast-feeding for mothers or infants. (14)

Monitoring and Laboratory Tests

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.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug

reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

IMOVAX® Rabies [Rabies Vaccine Inactivated (DCO)] has been studied in recent randomized controlled trials in both children (N=199) (15) using pre-exposure schedule (3 doses, I.M. plus booster at 1 year) and adults (N=124) (16) using the post exposure schedule (5 doses, I.M.). The most frequent adverse events were injection site pain and headache.

Table 3: Adverse Reactions Information (Clinical Trials)

Body System	Frequency	Adverse Reactions (Clinical Trials, N= 323)
Blood and lymphatic system disorders	Common (>1%, <10%)	Adenopathy
Immune system disorders	Common (>1%, <10%)	Allergic reaction such as urticaria, rash, dyspnea, wheezing
Nervous system disorders	Very Common (>1/10) Common (>1%, <10%)	Headache Dizziness
Gastrointestinal disorders	Very Common (>1/10) Common (>1%, <10%)	Nausea Abdominal pain, vomiting, diahrrea
Musculoskeletal and connective tissue disorders	Very Common (>1/10) Common (>1%, <10%)	Myalgia Arthralgia
General disorders and administration-site condition	Very Common (>1/10) Common (>1%, <10%)	Injection site pain, erythema, induration, malaise, injection site hematoma Injections site pruritus, fever, chills

Post-Market Adverse Drug Reactions

Based on spontaneous reporting, the following additional adverse events have been reported very rarely (>1/10,000) during the post marketing surveillance of IMOVAX® Rabies. Their frequencies have been estimated using number of reports and estimated number of patients. However, exact incidence cannot be precisely calculated.

Table 4: Adverse Reactions Information (Post-Marketing)

Body System	Adverse Reactions (Only Observed in Post-approval Use)
Immune system disorders	Pruritus, oedema Anaphylactic reactions, Serum sickness type reaction*
Nervous system disorders	Paraesthesia, neuropathy†
General disorders and administration-site condition	Asthenia

* Allergic reactions occurred less frequently among persons receiving primary vaccination. These reactions have been associated with the presence of betapropiolactone-altered human albumin in the HDCV.

† The use of corticosteriods to treat life-threatening neuroparalytic reactions carries the risk of inhibiting the development of active immunity to rabies. It is especially important in these cases that the serum of the patient be tested for rabies antibodies.

Two cases of neurologic illness resembling Guillain-Barré syndrome, (17) (18) a transient neuroparalytic illness, that resolved without sequelae in 12 weeks and a focal subacute central nervous system disorder temporally associated with HDCV, have been reported. (19)

DRUG INTERACTIONS

Corticosteroids and other immunosuppressive agents can interfere with the development of active immunity (See WARNINGS AND PRECAUTIONS – Immune).

Under no circumstances should rabies vaccine be administered in the same syringe or at the same site as rabies immune globulin.

If any other vaccines are administered during the same visit, they must be given at separate sites and with separate syringes. IMOVAX® Rabies [Rabies Vaccine Inactivated (DCO)] must not be mixed in the same syringe with other parenterals.

DOSAGE AND ADMINISTRATION

Recommendations for passive and/or active vaccination after exposure to an animal suspected of having rabies have been outlined by the WHO (4) and by the National Advisory Committee on Immunization. (1)

IMOVAX® Rabies [Rabies Vaccine Inactivated (DCO)] is indicated for 3-dose pre-exposure and 5-dose post-exposure series in combination with rabies immune globulin

for individuals suspected of exposure to rabies, with one exception: persons who have been previously vaccinated with IMOVAX® Rabies Vaccine in a pre-exposure or post-exposure treatment series should receive only vaccine.

Needles should not be recapped and should be disposed of properly.

Pre-Exposure Dosage:

Primary Vaccination

Three doses of IMOVAX® Rabies are required. One dose of 1.0 mL is to be given intramuscularly on each of days 0, 7 and 21.

Booster Doses

The booster dose of 1.0 mL of vaccine should be administered intramuscularly. (1)

Post-Exposure Immunization of Previously Unimmunized Individuals

A series of five doses of 1.0 mL of IMOVAX® Rabies should be given. The first 1.0 mL dose on day 0 as soon as possible after exposure, and one 1.0 mL dose on each of days 3, 7, 14 and 28 after the first dose. An appropriate dose of RIG should also be given on day 0 as described below.

RIG: The recommended dose of human RIG is 20 IU/kg body weight. This formula is applicable to all age groups, including children. If anatomically feasible, the full dose of RIG should be thoroughly infiltrated in the area around and into the wounds. When more than one wound exists, each should be locally infiltrated with a portion of the RIG. See RIG package insert for precise information on the administration of RIG. Since vaccine-induced antibody begins to appear within 1 week, there is no value in administering RIG more than 8 days after initiating an approved vaccine course.

IMOVAX® Rabies and immune globulin should be used concurrently for optimum post-exposure prophylaxis against rabies, except in certain previously immunized persons, as indicated below.

Post-exposure Prophylaxis of Previously Immunized Individuals (1)

Post-exposure prophylaxis for persons who have previously received rabies vaccine differs according to which preparation of vaccine was received.

A. Two doses of 1.0 mL of IMOVAX® Rabies, one injected immediately and the other 3 days later, without RIG, are recommended for exposed individuals with the following rabies immunization history:

(i) Completion of an approved course of pre- or post-exposure prophylaxis with HDCV, a WHO approved cell-culture rabies vaccine or PCEC (Purified Chick Embryo Culture):

(ii) Completion of immunization with other types of rabies vaccine or with IMOVAX® Rabies according to unapproved schedules so long as neutralizing rabies antibody has been demonstrated in serum.

B. A complete course of IMOVAX® Rabies plus RIG is recommended for those who may have received rabies vaccines but do not fulfill the criteria listed in A. A serum sample may be collected before vaccine is given, and if antibody is demonstrated the course may be discontinued, provided at least two doses of IMOVAX® Rabies have been administered.

Serologic Testing and Booster Doses

Healthy persons immunized with an appropriate regimen will develop rabies antibodies, and therefore routine post-immunization antibody determinations are not recommended. Neutralizing antibodies develop 7-14 days after immunization and persist for at least 2 years.

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. Persons with continuing high risk of exposure, such as veterinarians, should have their serum tested for rabies antibodies every 2 years; others working with live rabies virus in laboratories or vaccine-production facilities and who are at risk of inapparent exposure should be tested every 6 months.

Those with inadequate titres should be given a booster dose of IMOVAX® Rabies. Persons previously immunized with other vaccines should be given sufficient doses of IMOVAX® Rabies to produce an adequate antibody response. (1)

Missed Dose

It is very important to complete the series of rabies vaccinations on time. Cases of rabies have been reported when the approved schedule was not followed.

Administration

Administer the vaccine **intramuscularly**. For adults and children, the vaccine should always be administered in the deltoid area. (5) (14) (20) (21) (22) In infants and small children, the anterolateral aspect of the thigh is also acceptable. The gluteal area should never be used for injections because administration of rabies vaccine in this area results in lower neutralizing antibody titres. (5) (23) For information on vaccine administration see the current edition of the Canadian Immunization Guide or visit the Health Canada website.

Under no circumstances should vaccine be administered in the same syringe or at the same site as RIG.

Reconstitution

Parenteral Products:

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
3 mL	1 mL	1 mL	≥2.5 IU

Before administration parenteral drug products should be checked visually for any deviation from normal appearance including container integrity. The syringe and its package should also be inspected prior to use for evidence of leakage, or a faulty tip seal. If evidence of such defects is observed, the syringe should not be used.

The reconstituted vaccine should be used immediately.

After use, any remaining vaccine and container must be disposed of safely, according to biohazardous waste guidelines.

Package with Two Needles

Attach the plunger and reconstitution needle to the syringe and reconstitute the freeze-dried vaccine by introducing the diluent provided into the vial of powder. Gently swirl the contents until completely dissolved. Withdraw the suspension from the vial into the syringe. Remove the reconstitution needle and replace it with an appropriate needle for intramuscular injection.

Package with Attached Needle

Reconstitute the freeze-dried vaccine in its vial with the diluent supplied in the syringe. Gently swirl the contents until completely dissolved.

OVERDOSAGE

Not documented.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Human diploid cell rabies vaccine (HDCV) together with RIG and local treatment are highly effective in preventing rabies in exposed individuals. No post-exposure HDCV failures have occurred in Canada or the United States. The most important immune response to rabies vaccines is antibodies to the G protein of the viral envelope. (24) Pre-exposure vaccination with potent rabies vaccines leads to the development of virus-neutralizing antibodies (VNAs). Vaccination also induces production of cytotoxic T cells, which have been shown to protect vaccinated mice in the absence of neutralizing antibodies.

STORAGE AND STABILITY

Store at 2° to 8°C (35° to 46°F).

Do not freeze. Product which has been exposed to freezing should not be used.

SPECIAL HANDLING INSTRUCTIONS

The vaccine should be used immediately after reconstitution. If the vaccine is not administered promptly, discard contents.

Do not use the vaccine after the expiration date.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form

IMOVAX® Rabies [Rabies Vaccine Inactivated (DCO)] is available in two presentations:

single dose vials of lyophilized vaccine with 1 mL of diluent (sterile water for injection) contained in a disposable syringe with two needles (1 x 25G x 16 mm and 1 x 25G x 25 mm).

or

single dose vials of lyophilized vaccine with 1 mL of diluent (sterile water for injection) contained in a disposable syringe with an attached needle.

The vial stoppers for the vial and plunger stoppers and needle shields for the syringes supplied with this product do not contain dry natural latex rubber.

Composition

Component	Quantity (per 1.0 mL dose)
Rabies virus (WISTAR Rabies PM/WI 38 1503-3M Strain)	≥2.5 IU
Human albumin	<100 mg
Neomycin	<150 µg
Phenol red	20 µg
Diluent	
Sterile water for injection	

The powder is homogenous and pinkish beige to orangey yellow. The diluent is a clear colourless liquid. After reconstitution, IMOVAX® Rabies is a clear or slightly opalescent red to purplish red suspension.

Full product monograph available on request.
Visit us at www.sanofipasteur.ca
Vaccine Information Service: 1-888-621-1146 or 416-667-2779.
Product information as of November 2005.

Manufactured by:
Sanofi Pasteur SA
Lyon, France

Distributed by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

R4-1105 Canada

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Human Diploid Cell Rabies Vaccine

Composition

Component	Quantity (per 1.0 mL dose)
Rabies virus (WISTAR Rabies PM/WI 38 1503-3M Strain)	≥2.5 IU
Human albumin	<100 mg
Neomycin	<150 µg
Phenol red	20 µg
Diluent	
Sterile water for injection	

Product Characteristics

IMOVAX® Rabies [Rabies Vaccine Inactivated (DCO)] produced by Sanofi Pasteur SA is a sterile, stable, freeze-dried suspension of rabies virus prepared from the Pitman Moore strain (PM/WI38 1503-3M) obtained from the Wistar Institute, Philadelphia, PA. The virus is harvested from infected MRC-5 human diploid cells, concentrated by ultrafiltration and is inactivated by beta-propiolactone.

The potency of one dose (1.0 mL) IMOVAX® Rabies is ≥2.5 IU of rabies antigen.

One dose of reconstituted vaccine contains less than 100 mg human albumin, less than 150 µg neomycin sulphate and 20 µg of phenol red indicator. The 1 mL syringe of diluent provided (Sterile Water for Injection) is used for reconstitution of product supplied in a one-dose vial. IMOVAX® Rabies is a freeze-dried pinkish beige to orangey yellow coloured vaccine. The diluent is a clear, colourless liquid. After reconstitution the vaccine is clear or slightly opalescent red to purplish red suspension.

Human diploid cell rabies vaccine (HDCV) together with Rabies Immune Globulin (RIG) and local treatment are highly effective in preventing rabies in exposed individuals. No post-exposure HDCV failures have occurred in Canada or the United States. The most important immune response to rabies vaccine is antibodies to the G protein of the viral envelope. (24) Pre-exposure vaccination with rabies vaccine leads to the development of virus-neutralizing antibodies (VNAs). Vaccination also induces production of cytotoxic T cells, which have been shown to protect vaccinated mice in the absence of neutralizing antibodies.

The exact mechanism of protection of humans through post-exposure vaccination is still unknown, although it is certain that VNAs play a major role in this system. Pre-exposure prophylaxis is administered for several reasons. First, although pre-exposure vaccination does not eliminate the need for additional therapy after a rabies exposure, it

simplifies therapy by eliminating the need for RIG and decreasing the number of doses of vaccine needed -- a point of particular importance for persons at high-risk for being exposed to rabies in areas where immunizing products might not be available or where they might be at high-risk for adverse reactions. (2) Second, pre-exposure prophylaxis might protect persons whose post-exposure therapy is delayed. Finally, it might provide protection to persons at risk for inapparent exposures to rabies. (5)

Rabies is a vaccine-preventable neurotropic viral disease. In humans there are two clinical presentations, furious (agitated) and paralytic (dumb) rabies. The former is more common and associated with the classical presentation that includes hydrophobia and/or aerophobia. Most patients die within a few days of the onset of symptoms. Paralytic rabies is less distinctive with a more protracted clinical course, associated with local paraesthesia and progressive flaccid paralysis. Regardless of the clinical presentation, once manifest, rabies is almost invariably fatal. (25)

Rabies is transmitted when the virus is inoculated into tissues. This occurs most commonly through bites, although when rabies virus from saliva or infected tissue contaminates cuts or wounds, transmission is possible. Rarely, transmission has been recorded when virus was inhaled, or infected corneal grafts or other organs (26) were transplanted into patients. Thus, two broad categories of exposure are recognized as warranting post-exposure prophylaxis, bite and non-bite. (See INDICATIONS AND CLINICAL USE.) (1)

After infection, the usual incubation period is 20 to 60 days, although it may vary from several days to years. The rabies virus can infect any mammal. In North America, it occurs mainly in certain wild terrestrial carnivore species and is spread by them to domestic livestock and pets. Over the past few years the number of animal rabies cases in Canada has been steadily increasing. There remain regional differences in the prevalence of animal rabies across the country, and the specific species infected in each region vary over time. Over the past few years the incidence of bat strain rabies across the country has increased, and of the last six human rabies cases in Canada, five followed exposure to bats. (1) (27)

World Health Organization (WHO) reports indicate that more deaths occur worldwide from rabies than from other common infections including: dengue fever, polio, meningococcal meningitis or Japanese encephalitis. (2)

CLINICAL TRIALS

The definition of a minimally accepted antibody titre varies among laboratories and is influenced by the type of test conducted. The World Health Organization (WHO) currently considers a minimal acceptable antibody titre to be 0.5 IU/mL. (4) The Canadian national rabies reference laboratory considers an acceptable antibody response to be a titre of $\geq$0.5 IU/mL by the rapid fluorescent-focus inhibition test (RFFIT). (1)

Pre-Exposure Immunization

High titre antibody responses to the IMOVAX® Rabies [Rabies Vaccine Inactivated (DCO)] made in human diploid cells have been demonstrated in trials conducted in England, (28) Germany, (29) (30) France (31) and Belgium. (32) Seroconversion was often obtained with only one dose. With two doses one month apart, 100% of the recipients developed specific antibody and the geometric mean titre of the group was approximately 10 (IU). (33)

The 3 dose pre-exposure schedule administered by the intramuscular route has been evaluated in several clinical studies. After the 3 dose primary series, all vaccinees reached the serum antibody titre >0.5 IU/mL considered by WHO to confer protection.

Study Demographics and Trial Design - Pre-exposure

Table 5: Summary of Patient Demographics for Clinical Trials in Pre-exposure

Study #	Trial design	Dosage, route of administration and duration	Study subjects (number)	Mean age (Range)
(Study #1) (34)	Randomized open	1.0 mL I.M. days 0, 7, 28, (365)	32	adult
(Study #2) (33)	Randomized open	1.0 mL I.M. days 0, 7, 28	19	adult

In a clinical trial conducted in France (Study #1), thirty-two persons at occupational risk for rabies received IMOVAX® Rabies on Days 0, 7 and 28 and a booster one year later. A ten-year follow-up in 17 patients who received the 3-injection protocol followed by a booster dose at 1 year has shown the maintenance of seroconversion up to 5 years in 96.2%.

Serology was done annually and individuals who tested negative received a booster dose of vaccine.

Table 6: Rabies Titres Following Pre-Exposure Series, (Study #1) (34)

Primary Endpoints	Number of Subjects	% Seroconversion (95% CI)	GMT (95% CI) IU/mL
Day 42	32	100	33.6 (26.7-42.3)
Day 365 (pre-booster)	31	100	2.9 (2.2-3.8)
Day 379	30	100	54.1 (41.4-70.6)
Year 1		100	13.9 (9.6-20.0)
Year 2		100	9.5 (6.2-14.5)
Year 3		96.2 (88.8-100)	15.0 (9.9-22.6)
Year 5	19	96.2 (88.8-100)	11.3 (7.4-17.2)

In a clinical trial conducted in the US (Study #2), adults at occupational risk of rabies were randomized to receive one of 4 regimens of rabies vaccine. One group of 19 received IMOVAX® Rabies, 1.0 mL I.M. on days 0, 7 and 28.

Table 7: Rabies Titres Following Pre-Exposure Series (Study #2) (33)

Primary Endpoints	GMT (range) IU/mL	
Day 49	12.87	(2.75-54.95)
Day 90	5.09	(1.84-12.39)

Study Demographics and Trial Design – Post-exposure

Table 8: Summary of Patient Demographics for Clinical Trials in Post-exposure or Simulated Post-exposure

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender M:F
Study #5 (35) (36)	Open – post-exposure	1.0 mL SC on days 0, 3, 7, 14, 30 and 90 with antiserum on day 0	45 (44 received antiserum)	(3 – 90 years)	
Study #3 (16)	Randomized, modified double-blind, controlled sham post-exposure	1.0 mL I.M. on days 0, 3, 7, 14, 28; concomitant HRIG*	124	26.5 (20.3-57.1)	1:1.6 (61.2% F)
Study #4 (37)	Randomized, double-blind, controlled sham post-exposure	1.0 mL I.M. on days 0, 3, 7, 14, 28; concomitant HRIG*	16	22.6 (18-28)	1:3
		1.0 mL I.M. on days 0, 3, 7, 14, 28; concomitant HTHRIG†	16	21.7 (18-28)	1:7

* Human Rabies Immune Globulin

† Heat Treated Human Rabies Immune Globulin

Post-exposure efficacy of IMOVAX® Rabies was successfully proven during clinical experience in Iran. (35) (36) Forty-five persons age 3 to 90 years who had been severely bitten by rabid dogs or wolves received 1.0 mL of IMOVAX® Rabies on each of days 0, 3, 7, 14, 30 and 90 and heterologous rabies antiserum (40 IU/kg) on day 0 (44 persons). Post-exposure prophylaxis was begun within hours of or up to14 days after the bites. All individuals were fully protected against rabies and all developed rabies antibodies. (36) All persons, with the exception of a 90 year-old who died from unrelated causes, were healthy one year later. No rabies developed in the 27 persons with whom contact was maintained for four years after rabies exposure. (38)

Table 9: Rabies titres following post-exposure series (Study #5) (40) (42)

Primary Endpoints	Day 0	Day 3	Day 7	Day 14	Day 30	Day 90	Day 100
Mean antibody titres (IU/mL) N=45	0	0.74	1.1	10.7	48.9	46.3	320.7

In a randomized, modified double-blind multicentre study simulating the post exposure regimen, 124 subjects received 1.0 mL of IMOVAX® Rabies given intramuscularly on days 0, 3, 7, 14 and 28 and human rabies immunoglobulin on day 0. Other study groups received an investigational rabies vaccine. All vaccinees reached a serum antibody titre ≥ 0.5 IU/ml, considered by WHO to confer protection, by day 14 and remained at that level through day 90. One year later, the protection was maintained in 98.3% of subjects. (16)

Table 10: Rabies Titres Following Sham Post-Exposure Series (Study #3) (16)

	Immunogenicity				
Days after first dose	**Number of subjects**	**GMT (IU/mL) (95% CI)**		**Seroconversion % (95% CI)**	
0	124	0.025	(0.025-0.025)	0	(0-2.9)
7	124	0.18	(0.16-0.19)	4.03	(1.3-9.2)
14	124	10.3	(8.8-12.1)	100	(97.1-100)
28	124	20.5	(17.8-23.7)	100	(97.1-100)
42	124	29.4	(25.8-33.5)	100	(97.1-100)
90	121	15.4	(13.1-18.1)	100	(97.0-100)
180	119	7.2	(6.1-8.6)	99.2	(95.2-100)
365	116	3.7	(3.1-4.5)	98.3	(93.9-99.8)

In a clinical trial (Study #4) conducted to evaluate a new rabies immune globulin, 64 healthy adults received either human rabies immune globulin or human rabies immune globulin and IMOVAX® Rabies to simulate the post-exposure setting. In the vaccine groups, the antibody titres rose markedly from day 7 and reached a maximum value at day 14. All subjects who received RIG and vaccine maintained a protective level through day 42. No significant difference in immunogenicity results between the two groups receiving vaccine was observed. (37)

Table 11: Rabies Titres Following Sham Post-Exposure Series (37)

Primary Endpoints	Number and % of subjects with protective antibody levels					
	IMOVAX® Rabies + HRIG*			IMOVAX® Rabies + HTHRIG†		
	n	%	95% CI	n	%	95% CI
Day 0 (before immunization)	0	0	0-22	0	0	0-22
Day 3	1	6.7	0.2-32	0	0	0-22
Day 7	3	20	4.3-48	2	13.3	1.7-41
Day 14	15	100	78-100	15	100	78-100
Day 28	15	100	78-100	15	100	78-100
Day 35	15	100	78-100	15	100	78-100
Day 42	15	100	78-100	15	100	78-100

* Human Rabies Immune Globulin

† Heat Treated Human Rabies Immune Globulin

Pediatrics

A post-exposure experience in children from Thailand used IMOVAX® Rabies in 50 children aged below 13 years, 27 children were below 6 years of age with the youngest 12 months of age. There were no treatment failures. (7)

DETAILED PHARMACOLOGY

Data in animals, including single dose and repeated dose studies revealed no unexpected findings and no target organ toxicity. (39)

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Full product monograph available on request.
Visit us at www.sanofipasteur.ca
Vaccine Information Service: 1-888-621-1146 or 416-667-2779.

Product information as of November 2005.

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Sanofi Pasteur SA
Lyon, France

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R4-1105 Canada

sanofi pasteur

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

PART III: CONSUMER INFORMATION

IMOVAX® Rabies

Rabies Vaccine Inactivated (DCO)

ABOUT THIS MEDICATION

What the medication is used for:

IMOVAX® Rabies is a vaccine used to prevent rabies. IMOVAX® Rabies is given to persons at high risk of exposure to rabies as a result of their employment, travel, hobbies, etc. It can also prevent the disease if it is given to a person after they have been exposed to rabies following an animal bite or other similar incident. This vaccine may be given to adults and children of any age.

Vaccination After an Exposure

Anyone who has been bitten, scratched or licked on an open wound or sore by an animal suspected of having rabies should get this vaccine. The vaccine should be given as soon as possible to everyone who has had contact with the animal.

Preventive Vaccination (No Exposure)

Rabies vaccine is indicated for pre-exposure vaccination of persons who are at high risk of contact with potentially rabid animals or the rabies virus. This includes, for example, certain laboratory workers, veterinarians, animal control and wildlife workers, spelunkers (cave explorers), hunters and trappers in high-risk areas and international travellers including children, who are likely to come in contact with animals in parts of the world where rabies is common or those intending to live or work in such areas.

What it does:

IMOVAX® Rabies causes your body to produce its own protection against the rabies virus. When you get a series of rabies vaccine injections, your immune system produces antibodies against the virus in the vaccine. When you are have been in contact with the rabies virus, the antibodies will prevent rabies disease.

A series of shots is needed to protect you or your child against rabies.

When it should not be used:

Everyone should get the vaccine if there is a risk of getting rabies following contact with an animal.

For persons at risk of rabies because of their work, hobbies, or travel,

- IMOVAX® Rabies should not be administered to anyone with a history of hypersensitivity (allergy) and especially anaphylactic reactions to any component of IMOVAX® Rabies.
- If the person has a fever or serious illness delay the vaccination until the person is better. A person who has a minor illness accompanied by fever (example – a mild upper respiratory infection) may be vaccinated. Consult your doctor, nurse or pharmacist for guidance.

What the medicinal ingredient is:

Inactivated Rabies Virus (Diploid Cell Origin)

What the important nonmedicinal ingredients are:

Human albumin
Neomycin
Phenol red indicator

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:

Powder and Diluent for Suspension for Injection ≥2.5 IU/mL

WARNINGS AND PRECAUTIONS

BEFORE you or your child receives IMOVAX® Rabies talk to your doctor, nurse or pharmacist if you or your child:

- have a weakened immune system because of HIV/AIDS, cancer, or another disease that affects the immune system; treatment with drugs that affect the immune system such as steroids; cancer treatment with drugs or radiation.
- have any allergies to this vaccine or its ingredients or components of the container. (See Contraindications section.)

If you have been exposed to rabies virus, you should get the vaccine regardless of any other illnesses you may have.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with IMOVAX® Rabies include any drugs or treatments which may weaken the immune system.

IMOVAX® Rabies must not be mixed with other vaccines or medicinal products in the same syringe.

IMOVAX® Rabies must not be given at the same injection site as Rabies Immune Globulin.

PROPER USE OF THIS MEDICATION

Usual Dose

One dose of IMOVAX® Rabies is an injection of 1.0 mL.

Vaccination After an Exposure

A person who is exposed and has never been vaccinated against rabies should get 5 doses of rabies vaccine - one dose right away, and additional doses on the 3rd, 7th, 14th, and 28th days. He or she should also get injection(s) of Rabies Immune Globulin at the same time as the first dose. This gives immediate protection.

A person who has been previously vaccinated should get 2 doses of rabies vaccine - one right away and another on the 3rd day. Rabies Immune Globulin is not needed.

Pre-exposure

The pre-exposure schedule for rabies vaccination is 3 doses, given at the following times:

Dose 1: As appropriate
Dose 2: 7 days after Dose 1
Dose 3: 21 days after Dose 1

For laboratory workers, veterinarians and others who may be repeatedly exposed to rabies virus, periodic testing for immunity is recommended, and booster doses should be given as needed. Ask your doctor for details.

Rabies vaccine must be injected into the deltoid muscle (or into the thigh muscle in children under one year of age). There have been reports of vaccine failure (rabies) when the vaccine was injected into the buttocks.

Missed Dose:

It is very important to complete the series of rabies vaccinations on time. Cases of rabies have been reported when the approved schedule was not followed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

A vaccine, like any medicine, may cause serious problems, such as severe allergic reactions. The risk of IMOVAX® Rabies causing serious harm is extremely small.

Rabies vaccine cannot cause rabies because it does not contain any live virus.

Mild problems:

- pain, redness and swelling or itching where the needle was given (25%)
- headache, nausea, abdominal pain, muscle aches and dizziness (20%)

Moderate problems:

- hives, pain in the joints, fever (about 7% of booster doses)

Nervous system disorders have been reported after rabies vaccine, but this happens so rarely that it is not known if they are related to the vaccine.

This is not a complete list of side effects. For any unexpected effects while taking IMOVAX® Rabies, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

Store in a refrigerator at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Discard product if it has been exposed to freezing.

Do not use vaccine after expiration date.

The vaccine must be used immediately after mixing.

Keep out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, Health Canada collects information on serious and unexpected effects of vaccine(s). If you suspect you have had a serious or unexpected reaction to this vaccine you may notify Health Canada by:

Telephone: 613-952-6339
Fax 613-946-0224
By email: VAAES@phac-aspc.gc.ca

By regular mail:
The Vaccine Safety Unit
Immunization & Respiratory Infections Division
Centre for Infectious Disease Prevention & Control
Public Health Agency of Canada
PL 0602C Bldg #6, Tunney's Pasture
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician, nurse or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.sanofipasteur.ca or by contacting the sponsor, Sanofi Pasteur Limited,
1755 Steeles Avenue West, Toronto, Ontario, M2R 3T4.
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