AUSTRALIAN PRODUCT INFORMATION – MERIEUX INACTIVATED RABIES VACCINE, RABIES VIRUS (INACTIVATED)

1 NAME OF THE MEDICINE

Rabies Virus (Inactivated)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MERIEUX INACTIVATED RABIES VACCINE (MIRV) is lyophilised, stabilised suspension of inactivated Wistar rabies virus strain PM/W1381503-3M. It is cultured on human diploid cells and inactivated by ß-propiolactone. These human diploid cells are a cell line derived from human embryonic lung tissue in the 1960s.

The potency of the reconstituted vaccine is not less than 2.5 IU, the WHO International Standard per dose (1 mL).

Excipient with known effect: Neomycin

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

The powder is pinkish beige to orangey yellow. After reconstitution with the diluent supplied, MIRV is a clear or slightly opalescent red to purplish red suspension.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Pre-exposure immunisation in persons at special risk of contracting rabies. Post exposure immunisation against rabies.

4.2 DOSE AND METHOD OF ADMINISTRATION

One dose consists of 1 mL of vaccine administered by the intramuscular route, in the deltoid area for adults and children or the anterolateral area of the thigh muscle in infants and toddlers.

The vaccination schedule should be adapted in accordance with the circumstances of the exposure and the individual's rabies immune status. For further information, refer to the current Immunisation Handbook.

Product is for single use in one patient on one occasion only. Discard any residue.

Pre-Exposure Prophylaxis

- Primary vaccination: 3 injections at day 0, day 7, and day 21 or day 28

For further information about pre-exposure prophylaxis refer to the current Australian Immunisation Handbook.

Regular serology testing of neutralising antibodies is recommended to assess seroconversion of individuals at increased risk of exposure to rabies virus, with a frequency adapted to that risk. When antibody titre is below acceptable level, a booster dose is needed.

According to the Australian Immunisation Handbook, WHO current recommendations state that booster doses are not required for persons who are travelling to, or living in, an area of high rabies risk and who have completed a primary course, either pre- or post-exposure, using currently available cell culture derived vaccine.

Post-Exposure Prophylaxis

Post-exposure prophylaxis consists of local treatment of the wound, initiated as soon as possible after an exposure, followed by the administration of the vaccine and of passive immunisation, if indicated.

The vaccination must be administered under medical supervision and should be started as soon as possible after exposure.

The immunisation schedule must be adapted according to the type of contact and the immunisation status of the subject. For further information, refer to the current Australian Immunisation Handbook.

Vaccination of Non-Immunised Individuals

Administration of immunoglobulin

In the case of severe types of exposure, rabies immunoglobulin should be given in association with the vaccine for non-immunised individuals:

On day 0, a complementary passive immunisation is required using:

- Human rabies immunoglobulin (HRIG) 20 IU/kg body weight

As much as possible should be infiltrated around the wounds. The remainder should be administered by deep intramuscular injection at a site distant from the vaccine injection site. If possible, the vaccine should be injected contra-laterally to the immunoglobulin administration sites.

Administration of vaccine

Vaccine should be administered on day 0, day 3, day 7 and day 14 (4 injections of 1 mL). The posology is the same for adults and children.

Vaccination of Previously Immunised Individuals (full pre-exposure prophylaxis vaccination confirmed)

In this case, administration of immunoglobulin is not required. Two injections of vaccine should be administered at day 0 and day 3.

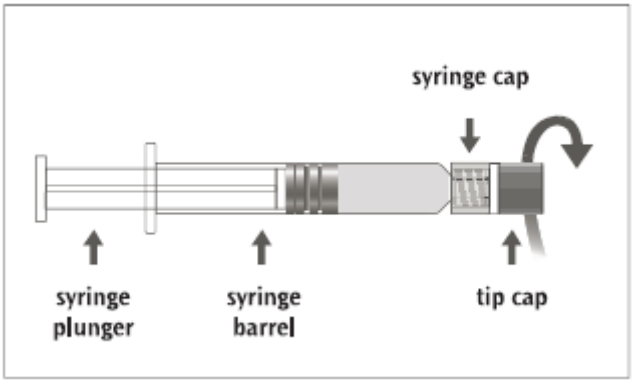
This schedule should not apply to immunocompromised individuals.

In both previously-immunised and non-immunised individuals, consideration should also be given to the possibility of tetanus and other wound infections, and appropriate measures taken as per the current Australian Immunisation Handbook.

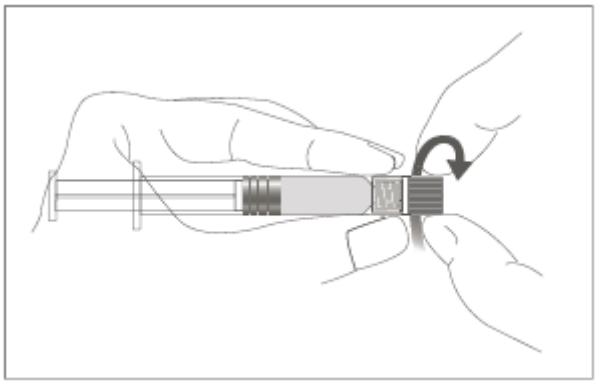
Method of Administration

Preparation

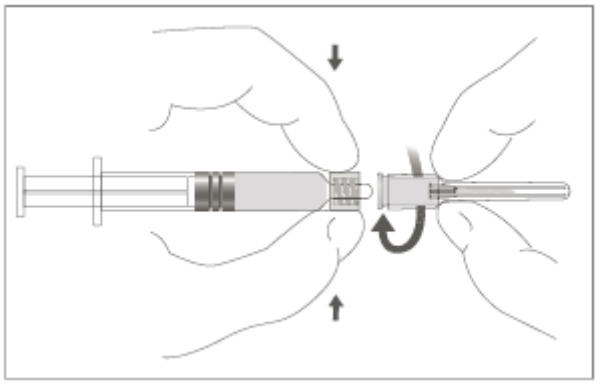
Instructions for Luer-Lok™ syringe



Step 1: Holding the syringe cap in one hand (avoid holding the syringe plunger or barrel), unscrew the tip cap by twisting it counter-clockwise.



Step 2: To attach the needle to the syringe, gently twist the needle clockwise into the syringe until slight resistance is felt.



Reconstitution of vaccine (all syringes):

Reconstitute the freeze-dried vaccine by introducing the diluent in the pre-filled syringe into the vial of powder. Gently swirl until complete suspension of the powder is obtained.

Syringe with attached needle

Withdraw the suspension from the vial into a separate syringe, and administer via intramuscular injection with an appropriate needle for each individual.

Luer-LokTM syringe

Without removing the needle from the vial, unscrew the syringe to eliminate negative pressure (as the vial is sealed under vacuum). Reattach the needle remaining in the vial to the syringe (as per step 2). Withdraw the suspension from the vial into the syringe. Unscrew the reconstitution needle and replace it with a sterile needle (as per step 2) of an appropriate size and length for intramuscular injection.

Once reconstituted, the vaccine must be used immediately.

After use, any remaining vaccine and container must be disposed of safely, preferably by heat inactivation or incineration, according to locally agreed procedures.

4.3 CONTRAINDICATIONS

Pre-Exposure Prophylaxis

Known systemic hypersensitivity reaction to any component of MIRV or after previous administration of the vaccine or a vaccine containing the same components.

Vaccination must be postponed in case of febrile or acute disease.

Post-Exposure Prophylaxis

Since rabies infection generally results in death, there are no contraindications to post-exposure vaccination.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Do not administer intravenously or intradermally.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following administration of the vaccine.

As with any vaccine, vaccination with MIRV may not protect 100% of vaccinated individuals.

The full course of immunisation should be completed in order to obtain efficient antibody response to prevent rabies.

Neomycin

As each dose may contain undetectable traces of neomycin which is used during vaccine production, caution must be exercised when the vaccine is administered to individuals with hypersensitivity to this antibiotic and other antibiotics of the same class.

Immunocompromised individuals

In individuals with congenital or acquired immunodeficiency, the immune response to the vaccine may be inadequate.

Therefore, it is recommended to monitor serologically RVNA (Rabies Virus Neutralizing Antibodies) level in such individuals to ensure that an acceptable immune response has been induced. Additional doses should be given as necessary.

Moreover, if post-exposure prophylaxis is needed, only full schedule of vaccination should be administered. In addition, rabies immunoglobulin should be given in association with the vaccine for both categories II& III exposures.

Bleeding Disorders

Because intramuscular injection can cause injection site haematoma, MIRV should not be given to individuals with any bleeding disorder, such as haemophilia or thrombocytopaenia, or to individuals on anticoagulant therapy unless the potential benefits clearly outweighs the risk of administration. If the decision is made to administer MIRV in such individuals, it should be given with caution, with steps taken to avoid the risk of haematoma formation following injection.

Apnoea

The potential risk of apnoea and the need for respiratory monitoring for 48-72 hours should be considered when administering the primary immunisation series to very premature infants

(born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance and paresthesia. It is important that procedures are in place to avoid injury from fainting.

Use in the elderly

MIRV is indicated for use in elderly.

Paediatric use

MIRV is indicated for use in paediatric population.

Effects on laboratory tests

Interference of MIRV with laboratory and/or diagnostic tests has not been studied.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Immunosuppressive treatments, including long-term systemic corticosteroid therapy, may interfere with antibody production and cause the failure of the vaccination. It is therefore advisable to perform a serological test (RVNA) level using a Rapid Fluorescent Focus Inhibition Test (RFFIT) 2 to 4 weeks after the last injection.

No clinical data are available regarding the concurrent administration of MIRV with other vaccines.

As rabies immunoglobulin interferes with development of immune response to the vaccine, the recommendation of administration of rabies immunoglobulin must be strictly followed.

Separate injection sites and separate syringes must be used in case of concomitant administration with any other medicinal product, including rabies immunoglobulins.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

MIRV has not been evaluated for impairment of male or female fertility.

Use in pregnancy (Category B2)

Pre-exposure

The vaccine has not been studied in animal teratogenicity studies. Data on the use of this vaccine in pregnant women are limited. Therefore, the administration of the vaccine during pregnancy is not recommended.

For the vaccination of individuals at a high risk of exposure, the risk/benefit ratio must be assessed before administering the vaccine.

Post-exposure

Due to the severity of the disease, pregnancy is not a contraindication.

Use in lactation

Pre-exposure

It is not known whether MIRV is excreted in human milk. Therefore, caution must be exercised when the vaccine is administered to a nursing woman.

Post-exposure

Due to the severity of the disease, lactation is not a contraindication.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive or use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse event information is derived from clinical trials and worldwide post-marketing experience.

Within each system organ class the adverse events are ranked under headings of frequency, using the following CIOMS frequency rating:

- Very common ≥ 10%;
- Common ≥ 1 and < 10%;
- Uncommon ≥ 0.1 and < 1%;
- Rare ≥ 0.01 and < 0.1%;
- Very rare < 0.01%;
- Not known (cannot be estimated from available data).

Data from Clinical Studies

In clinical studies, more than 1,600 subjects (from less than 1 through 72 years of age) received at least one dose of MIRV.

A pooled analysis has been performed on 4 randomized, controlled, observer-blind clinical studies sharing the same safety standards, integrating data from 401 subjects (113 children and adolescents from 2 through 17 years of age and 288 adults from 18 through 65 years of age). In two studies in adults, the subjects received HRIG concurrently with the first dose of MIRV.

The adverse reactions were generally of mild intensity and appeared within 3 days after vaccination. Most reactions resolved spontaneously within 1 to 3 days after onset. Most frequent adverse reactions events in all age groups were injection site pain, and headache, malaise and myalgia.

The table below presents the frequencies of solicited adverse reaction (recorded within 7 days) and unsolicited related adverse events (recorded within 28 days), reported following any dose of MIRV.

Subjects experiencing at least one:	**Adults 18 years and older**	**Children and Adolescents 2 through 17 years old**
Adverse Reactions	% † - Frequency	% † - Frequency
SOC: Blood and lymphatic system disorders		
Lymphadenopathy	Uncommon - 0.3 %	-
SOC: Gastrointestinal disorders		
Nausea	Common – 1.4%	-
Abdominal pain	Uncommon – 0.7%	-
Diarrhoea	Uncommon - 0.7 %	-
Vomiting	Uncommon - 0.3 %	-
SOC: General disorders and administration site condition		
Injection site pain	Very common- 58.5%	Very common- 39.8%
Malaise	Very common- 36.3%	Very common- 20.4%
Injection site erythema	Common – 4.5%	Common - 6.2%
Injection site swelling/induration	Common – 3.1%	Common - 5.3%
Fever	Common – 2.1%	Common – 7.1%
Injection site pruritus	Common – 1.4%	Uncommon - 0.9%
Injection site hematoma/ bruising	Common – 1.4%	Uncommon - 0.9%
Fatigue/ Asthenia	Common – 1.0%	-
Chills	Uncommon - 0.3 %	-
SOC: Nervous system disorders		
Headache	Very common- 38.1%	Very common- 28.3%
Dizziness	Uncommon - 0.7 %	Uncommon - 0.9 %

Subjects experiencing at least one:	Adults 18 years and older	Children and Adolescents 2 through 17 years old
Paresthesia	Uncommon - 0.3 %	-
SOC: Musculoskeletal and connective tissue disorders		
Myalgia	Very common- 44.3%	Very common- 13.3%
SOC: Immune system disorders		
Allergic reaction with skin disorders or respiratory manifestations	Uncommon - 0.3 %	-

†: For each reaction, the frequency has been defined by the number of subjects experiencing the reaction divided by the number of subjects with available data.

For a comprehensive overview of vaccine safety, additional relevant adverse reactions from studies not eligible for pooled safety analysis have been included. Their frequency is estimated based on total number of subjects from clinical development (N= 1674 subjects, including at least 612 children and adolescents).

Subjects experiencing at least one:	Adults 18 years and older	Children and Adolescents 2 through 17 years old
Adverse Reactions	Frequency	Frequency
SOC: Musculoskeletal and connective tissue disorders		
Arthralgia	Uncommon	Uncommon
SOC: Immune system disorders		
Angioedema	Rare	-

Data from Post-Marketing Experience

Based on spontaneous reporting, the following additional adverse events have been reported during the commercial use of MIRV. These events have been very rarely reported, however, exact incidence rate cannot be precisely calculated, their frequency is qualified as "Not known".

Immune system disorders

- Anaphylactic reactions
- Serum sickness type reactions: These reactions might be associated with the presence of betapropiolactone-altered human albumin in the Human Diploid Cell Vaccine (HDCV).

Nervous system disorders

- Neuropathy
- Convulsion, encephalitis

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems (Australia) or https://nzphvc.otago.ac.nz/reporting/ (New Zealand).

4.9 OVERDOSE

For general advice on overdose management, contact the Poisons Information Centre, telephone number 13 11 26 (Australia) or the National Poisons Centre, 0800 POISON or 0800 764 766 (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: ANTIINFECTIVES FOR SYSTEMIC USE, ATC code: J07BG01

Mechanism of action

Following a single deep subcutaneous injection, an antibody response can be detected after a variable period of up to 7 days, in all subjects. Peak antibody levels are reached at about 30 days and then start to decline.

Clinical trials

No pharmacodynamic studies are performed for vaccines.

5.2 PHARMACOKINETIC PROPERTIES

No pharmacokinetics studies are performed for vaccines.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

MIRV has not been evaluated for genotoxic potential.

Carcinogenicity

MIRV has not been evaluated for carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each vial contains, in addition, between 100 and 150 microgram of neomycin and up to 70 mg of albumin.

The manufacture of this product includes exposure to bovine materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

6.2 INCOMPATIBILITIES

This vaccine must not be mixed with other medicinal products.

6.3 SHELF LIFE

36 months when stored at 2° to 8°C.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store refrigerated (2° to 8°C). Do not freeze. Use immediately after reconstituting the vaccine.

6.5 NATURE AND CONTENTS OF CONTAINER

Powder (1 dose) in vial (glass) and 1.0 mL of diluent (water for injection) in pre-filled syringe (glass) with attached needle or pre-filled needlelesss (Luer-lok) syringe with Plastic Rigid Tip Cap.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

After use, any remaining vaccine and container must be disposed of safely, preferably by heat inactivation or incineration, according to locally agreed procedures.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Australia:
sanofi-aventis australia pty ltd
12 – 24 Talavera Road
Macquarie Park NSW 2113
Australia
1800 818 806

New Zealand:
sanofi-aventis new zealand limited
Level 8
56 Cawley St
Ellerslie
Auckland
New Zealand
0800 283 684

9 DATE OF FIRST APPROVAL

21 October 1991

10 DATE OF REVISION

28 April 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformat in line with the new TGA template
1; 4; 5; & 6	Editorial
4.2	Addition of instructions
4.4	Addition of text for ease of readability and the addition of Apnea and Anxiety-relates reactions as warnings and precautions
4.6	Information regarding use in lactation in post-exposure prophylaxis added
4.8	Revision of Adverse Effects (undesirable effects) and Post Marketing Experience
5.1	ATC code, Pharmacotherapeutic code, and Pharmacodynamic added
6.2	Warning regarding incompatibility added
6.5	Addition of information regarding immediate container for the medicine
6.6	Information regarding disposal added
8	Revision of sponsor details