

PRIORIX® PRODUCT INFORMATION
Measles, mumps and rubella vaccine live

DESCRIPTION

PRIORIX is a live virus vaccine for immunisation against measles, mumps and rubella.

PRIORIX is a sterile lyophilised mixed preparation containing the attenuated Schwarz measles virus strain, the RIT 4385 strain of mumps virus (derived from the Jeryl Lynn strain) and the Wistar RA 27/3 rubella virus strain. Each virus strain is separately obtained by propagation in either chick embryo tissue cultures (mumps and measles) or MRC5 human diploid cells (rubella).

PRIORIX is presented as a whitish to slightly pink powder for reconstitution with sterile Water for Injection diluent.

Each 0.5 mL dose of the reconstituted vaccine contains not less than $10^{3.0}$ CCID₅₀ (cell culture infectious dose 50%) of the Schwarz measles, not less than $10^{3.7}$ CCID₅₀ of the RIT 4385 mumps and not less than $10^{3.0}$ CCID₅₀ of the Wistar RA 27/3 rubella virus strains. The three virus strains are mixed prior to lyophilisation. The lyophilised vaccine also contains lactose, amino acids and sorbitol and mannitol as stabilisers. Neomycin sulphate is present as a residual from the manufacturing process.

The manufacture of this product includes exposure to bovine derived 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.

PRIORIX meets the World Health Organisation requirements for manufacture of biological substances and for measles, mumps and rubella vaccines and combined vaccines (live).

CLINICAL PHARMACOLOGY

PRIORIX induces antibodies against all vaccine components.

Clinical Trials

Seroconversion has been shown to equate with protection against each of the measles, mumps and rubella viruses.

Primary Immunisation:

In clinical studies, PRIORIX has been demonstrated to be highly immunogenic.

In previously seronegative vaccinees, antibodies were detected in 98.0%, 96.1% and 99.3% of subjects against measles, mumps and rubella respectively.

In a pooled analysis of comparative studies of over 1400 children, antibodies against measles, mumps and rubella were detected in 98.7%, 95.5% and 99.5% of previously seronegative subjects (n=1094) who received PRIORIX. Antibodies against measles, mumps and rubella were detected in 96.9%, 96.9% and 99.5% of subjects (n=388) respectively, who had received a commercially available combined MMR vaccine.

Similar seroconversion rates were seen in subjects who received PRIORIX by the intramuscular route.

Seroconversion rates in a limited number of subjects (n=60) aged 9-11 months were also measured. 100% of these subjects developed antibodies against mumps and rubella. 96.6% of the subjects developed anti-measles antibodies.

Antibody levels of participants in the pooled studies have been monitored for up to 12 months following vaccination. All subjects remained seropositive for anti-measles and anti-rubella antibodies. Anti-mumps antibodies were detected in 88.4% of subjects. A similar result was observed with a commercially available MMR vaccine.

In a more recent study comparing the current formulation of PRIORIX (albumin-free) with the previous formulation containing albumin, antibodies against measles, mumps and rubella were detected in 98.4, 94.8 and 100% of previously seronegative subjects (n=191) who received the current formulation. Antibodies against measles, mumps and rubella were detected in 99.5, 94.7 and 100% of subjects (n=190) respectively, who had received the formulation used in the earlier studies containing albumin. There were no significant differences in immunogenicity between the current formulation of PRIORIX (albumin-free) and the formulation containing albumin used in the earlier studies.

Booster Immunisation:

A booster dose of PRIORIX was administered to children aged 4 - 6 years or 11-12 years, who had been primed with a different MMR vaccine. All subjects aged 4-6 years who were seronegative at the time of booster, subsequently seroconverted. In subjects aged 11 -12 years who were seronegative at the time of booster, seroconversion rates of 85.7%, 93.5% and 100% were observed for measles, mumps and rubella respectively.

INDICATIONS

PRIORIX is indicated for active immunisation against measles, mumps and rubella.

The Australian NH&MRC Immunisation Handbook recommendations for MMR vaccination are as follows:

MMR vaccine is recommended for all children at 12 months of age and again at 4-6 years of age unless there is a genuine contraindication.

In populations with a high incidence of early measles, vaccination at 9 months of age is recommended. Because of the risk to Aboriginal children, the Northern Territory health authority has adopted a practice of administering the first dose of MMR vaccine to Aboriginal children at the age of 9 months. This conforms with WHO recommendations for such populations. The second dose is given at 4 - 6 years.

Unimmunised children in the following groups are at particular risk from severe measles infection:

- children with chronic conditions such as cystic fibrosis, congenital heart or kidney disease, failure to thrive, Down Syndrome,
- children from the age of 1 year upwards in child care centres, family day care and playgroups,
- children living in institutions, and
- Aboriginal and Torres Strait Islander children.

HIV-positive individuals who do not have impaired immunity may be given measles, mumps, rubella combined vaccines in the absence of other contraindications.

CONTRAINDICATIONS

It is contraindicated to administer PRIORIX to pregnant women (See *Use in Pregnancy*). If vaccination of postpubertal women occurs, pregnancy should be avoided for three months.

PRIORIX should not be administered to subjects with known hypersensitivity to any components of the vaccine (for egg allergy see *Precautions*). Vaccination is contraindicated in children who are allergic to neomycin, although a history of contact dermatitis to neomycin is not a contraindication.

PRIORIX is contraindicated in subjects having shown signs of hypersensitivity after previous administration of measles, mumps and/or rubella vaccines.

As with other vaccines, the administration of PRIORIX should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, is not a contraindication.

PRIORIX should not be given to subjects with impaired immune responses. These include patients with primary or secondary immunodeficiencies, those with untreated malignant disease and those receiving immunosuppressive or X-ray therapy or high dose steroids (equivalent to 2mg/kg/day prednisolone).

However, measles, mumps, rubella combined vaccines can be given to asymptomatic HIV-infected persons without adverse consequence to their illness, and may be considered for those who are symptomatic.

PRECAUTIONS

PRIORIX must not be administered intravascularly.

As with all injectable vaccines, appropriate medical treatment (i.e. adrenaline) and supervision should always be readily available in case of anaphylactic reactions following the administration of the vaccine.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Alcohol and other disinfecting agents must be allowed to evaporate from the skin before injection of the vaccine as they can inactivate the attenuated viruses in the vaccine.

Infants below 12 months of age may not respond sufficiently to the measles component of the vaccine due to the possible persistence of maternal measles antibodies. This should not preclude the use of the vaccine in younger infants (< 12 months) as vaccination may be indicated in certain situations such as high risk areas (see *Indications*). In these circumstances revaccination at or after 12 months should be considered.

Limited protection against measles may be obtained by vaccination up to 72 hours after exposure to natural measles. If the vaccination status of the child is in doubt, the vaccine should be given as there are no ill effects of vaccinating individuals who are already immune. The antibody response to the rubella and mumps components is too slow for effective post-exposure prophylaxis.

Transmission of measles and mumps virus from vaccinees to susceptible contacts has never been documented. Pharyngeal excretion of the rubella virus is known to occur about 7 to 28 days after vaccination with peak excretion around the 11th day. However there is no evidence of transmission of this excreted virus to susceptible contacts.

PRIORIX should be given with caution to persons with a history or family history of allergic disease or those with a history or family history of convulsions.

The measles and mumps components of the vaccine are produced in chick embryo cell culture and may therefore contain traces of egg protein. 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 vaccinated with PRIORIX.

It appears that persons are not at increased risk if they have egg allergies that are not anaphylactic or anaphylactoid in nature. Such persons may be vaccinated in the usual manner. There is no evidence to indicate that persons with allergies to chickens or feathers are at increased risk of reaction to the vaccine.

As for any vaccine, immunisation with measles, mumps, rubella vaccine may not result in seroconversion in 100% of susceptible persons given the vaccine.

Cases of worsening thrombocytopenia and recurrence of thrombocytopenia in subjects who suffered thrombocytopenia after the first dose have been reported following vaccination with live measles, mumps and rubella vaccines. In such cases, the risk-benefit of immunising with PRIORIX should be carefully evaluated.

Use in Pregnancy (Category B2):

It is contraindicated to administer PRIORIX to pregnant women. Pregnancy should be avoided for three months after vaccination (see *Contraindications*).

The Australian Medicines in Pregnancy handbook (3rd edition) states that: Currently available live virus vaccines have not caused teratogenic effects in humans. Caution needs to be exercised as live virus vaccines have been shown to cross the placenta and infect the foetus. Some live virus vaccines have caused birth defects in animals. (The NH&MRC publication "Immunisation Procedures" should be consulted for more comprehensive information.)

Women of child bearing age should be tested for rubella antibodies prior to pregnancy. All seronegative women, provided they are not pregnant, should be offered rubella vaccine. Those administering the vaccine should be careful to instruct women to whom it is given that they should not become pregnant for at least two full menstrual cycles because rubella vaccine can cause foetal infection. However, to date, there have not been any rubella-like birth defects in the live born infants (about 400) of seronegative mothers vaccinated during or just before pregnancy. Based on this experience, the rubella vaccine cannot be considered teratogenic during pregnancy and need not be the reason to recommend termination of pregnancy. The final decision must be made by the patient and her physician.

Use in Lactation:

There is little human data regarding use in breastfeeding women. Persons can be vaccinated where the benefit outweighs the risk.

INTERACTIONS WITH OTHER MEDICINES

Although data on concomitant administration of PRIORIX and other vaccines have not been obtained, it is accepted that measles, mumps and rubella combined vaccines may be given at the same time as oral polio vaccine (OPV), inactivated polio vaccine (IPV), combined diphtheria, tetanus and pertussis vaccines (acellular or whole-cell), hepatitis B vaccines and *Haemophilus influenzae* type b vaccines (Hib), as long as separate sites and separate syringes are used.

If PRIORIX cannot be given at the same time as another live attenuated vaccine, an interval of at least 1 month should be left between the two vaccinations.

If tuberculin (Mantoux) testing is needed, it should be carried out before, or simultaneously with measles, mumps and rubella vaccination. It has been reported that live measles (and possibly mumps) vaccine may cause a temporary depression of tuberculin skin sensitivity which could last 4 to 6 weeks. Tuberculin testing is therefore unreliable (false negative) for 4 to 6 weeks after administration of measles, mumps, rubella vaccine.

In subjects who have received human gammaglobulins or blood transfusions, vaccination should be delayed for at least 3 months because of the possibility of vaccine failure due to passively acquired measles, mumps and rubella antibodies.

PRIORIX should not be mixed with other vaccines in the same syringe.

PRIORIX can be used as a booster dose in subjects who have previously been vaccinated with PRIORIX or another measles, mumps and rubella combined vaccine.

ADVERSE EFFECTS**Clinical Trial Experience****Primary Immunisation:**

A total of approximately 12,000 subjects were administered PRIORIX in clinical trials. During controlled clinical studies, the signs and symptoms were actively monitored during a 42 day follow-up. The vaccinees were also requested to report any other clinical events which manifested during the study period. The following table lists the pooled incidence of solicited symptoms from 9

comparative studies for children vaccinated with PRIORIX according to protocol. (The results for the comparator vaccine are based on 8 studies, n=1074).

| Solicited Symptom | Priorix (% incidence) | Comparator vaccine (% incidence) |
|---------------------|-----------------------|----------------------------------|
| Local redness | 7.2 | 16.3 |
| Rash* | 7.1 | 9.8 |
| Fever (>39.5°C)* | 6.4 | 11.9 |
| Local pain | 3.1 | 8.6 |
| Local swelling | 2.6 | 7.4 |
| Parotid swelling | 0.7 | 0.5 |
| Febrile convulsions | 0.1 | 0.1 |

* Daily incidence in two studies not recorded

Other events:

The safety profile presented below is based on a total of approximately 12,000 subjects administered PRIORIX in clinical trials. Causality has not been established. The incidence of adverse reactions described below were similar to the comparator MMR vaccine.

The events are listed within body systems and categorised by frequency according to the following definitions:

| | |
|--------------|--------------------|
| Very common: | ≥ 10% |
| Common: | ≥ 1% and < 10% |
| Uncommon: | ≥ 0.1% and < 1% |
| Rare: | ≥ 0.01% and < 0.1% |
| Very rare: | < 0.01% |

Body as a whole: *Very common:* redness at the injection site, fever ≥ 38°C (rectal) or ≥ 37.5°C (axillary/oral); *Common:* pain and swelling at the injection site, fever > 39.5°C (rectal) or >39°C (axillary/oral), viral infection; *Uncommon:* injury, infection, allergy, abnormal crying, fatigue, infection bacterial, infection fungal

Skin and appendages: *Common:* rash; *Uncommon:* dermatitis, eczema, pruritis, herpes simplex, herpes zoster

Respiratory: *Common:* pharyngitis, bronchitis, coughing, respiratory disorder, other upper respiratory tract infection, rhinitis; *Uncommon:* pneumonia, laryngitis, stridor

Gastrointestinal: *Common:* Diarrhoea; *Uncommon:* anorexia, gastrointestinal disorder, parotid gland enlargement, toothache, vomiting, enteritis, gastroenteritis, stomatitis, stomatitis aphthous

Central Nervous System: *Common:* nervousness; *Uncommon:* insomnia; *Rare:* febrile convulsions

Special Senses: *Common:* otitis media; *Uncommon:* conjunctivitis

Haematologic/ Lymphatic: *Uncommon:* anaemia, lymphadenopathy

Five adverse events experienced by three subjects were considered by the investigators to be serious and related or possibly related. These events were: granulocytopenia, fever, exanthema, vomiting and epididymitis.

Booster Immunisation:

In a study examining booster doses of PRIORIX administered to children aged 4-6 years, the following solicited symptoms were reported:

| Solicited symptom | Priorix (n=38) % incidence | Comparator vaccine (n=37) % incidence |
|--------------------------|---------------------------------------|--|
| Pain (burning/stinging)* | 13.2 | 32.4 |
| Pain | 10.5 | 18.9 |
| Redness | 10.5 | 8.1 |
| Swelling | 2.6 | 0.0 |
| Fever > 39.5°C | 5.3 | 0.0 |
| Parotid gland swelling | 0.0 | 0.0 |

* pain at the time of injection (burning/stinging) or within 30mins of injection

In a study examining booster doses of Priorix administered to children aged 11-12 years of age, the following solicited symptoms were reported:

| Solicited symptom | Priorix (n=149) % incidence | Comparator vaccine (n=150) % incidence |
|--------------------------|--|---|
| Pain | 20.1 | 33.3 |
| Redness | 25.5 | 25.3 |
| Swelling | 13.4 | 12.7 |
| Fever > 39.5°C | 1.3 | 0.7 |
| Skin rash | 0.7 | 1.3 |
| Parotid gland swelling | 1.3 | 0.7 |

Other events

All unsolicited events reported in this booster study, are listed below. The events are listed within body systems and categorised by frequency according to the following definitions:

Very common: $\geq 10\%$
Common: $\geq 1\%$ and $< 10\%$
Uncommon: $\geq 0.1\%$ and $< 1\%$
Rare: $\geq 0.01\%$ and $< 0.1\%$
Very rare: $< 0.01\%$

Causality has not been established.

Booster in 4-6 year old children:

Body as a whole: *Very common:* pain and redness at the injection site, fever $\geq 38^{\circ}\text{C}$ (rectal) or $\geq 37.5^{\circ}\text{C}$ (axillary/oral); *Common:* swelling at the injection site, fever $> 39.5^{\circ}\text{C}$ (rectal) or $>39^{\circ}\text{C}$ (axillary/oral), allergy

Respiratory: *Common:* bronchitis, coughing, pharyngitis, rhinitis; *Uncommon:* asthma, epistaxis, sinusitis

Gastrointestinal: *Common:* diarrhoea, vomiting; *Uncommon:* colitis, gastroenteritis, parotid gland enlargement

Central Nervous System: *Common:* headache; *Uncommon:* dysphonia

Skin and appendages disorder: *Common:* rash, eczema; *Uncommon:* dermatitis, urticaria

Vision disorders: *Uncommon:* conjunctivitis

Resistance mechanism disorders: *Common:* upper respiratory tract infection, otitis media, herpes zoster (varicella); *Uncommon:* herpes simplex, infection viral

Booster in 11-12 year old children

Body as a whole: *Uncommon:* viral infection, lymphadenopathy

Respiratory: *Common:* upper respiratory tract infection, rhinitis, pharyngitis, asthma; *Uncommon:* coughing, epistaxis

Gastrointestinal: *Uncommon:* abdominal pain, gastroenteritis, diarrhoea

Central Nervous System: *Common:* headache; *Uncommon:* dizziness

Skin and appendages disorder: *Uncommon:* pruritis, skin exfoliation, nail disorder, injection site reaction, urticaria

Post-marketing data

During post-marketing surveillance, the following reactions have been reported additionally in temporal association with PRIORIX vaccination:

Infections and infestations:

Rare: meningitis, measles-like syndrome, mumps-like syndrome (including orchitis, epididymitis and parotitis)

Blood and Lymphatic system disorders:

Rare: thrombocytopenia, thrombocytopenic purpura

Immune system disorders:

Rare: anaphylactic reactions

Nervous system disorders:

Rare: encephalitis, cerebellitis, cerebellitis like symptoms (including transient gait disturbance and transient ataxia), Guillain Barré syndrome, transverse myelitis, peripheral neuritis

Vascular disorders:

Rare: vasculitis (including Henoch Schonlein purpura and Kawasaki syndrome)

Skin and subcutaneous tissue disorders:

Rare: erythema multiforme

Musculoskeletal and connective tissue disorders:

Rare: arthralgia, arthritis

As in natural rubella infection, myalgia may occur 2 to 4 weeks after administration of live rubella vaccines.

Accidental intravascular administration may give rise to severe reactions or even shock. Immediate measures depend on the severity of the reaction. (see *Precautions*).

DOSAGE AND ADMINISTRATION

All parenteral drug and vaccine products should be inspected visually for any particulate matter and/or variation of physical aspects prior to administration.

The vaccine must be reconstituted by adding 0.5mL of sterile water diluent to the vial containing the powder of lyophilised vaccine. After the addition of the diluent to the powder, the mixture should be well shaken until the powder is completely dissolved in the diluent.

The vaccine should be injected as soon as possible after reconstitution. The reconstituted vaccine can be stored between 2 and 8°C, for up to 8 hrs before use.

Dosage

A reconstituted dose of 0.5mL is recommended for children and adults.

Children:

Two doses are usually given. The first dose is usually given at 12 months of age, followed by a booster dose at 4 - 6 years of age (see *Indications*).

Adults:

A single dose may be given to adults who do not have immunity.

Administration

PRIORIX is administered by subcutaneous or intramuscular injection. THE VACCINE SHOULD NEVER BE ADMINISTERED INTRAVASCULARLY.

The NH&MRC recommends that MMR vaccines should be administered into the anterolateral thigh of children under 12 months of age. The deltoid region is the preferred site of vaccination in older children and adults.

OVERDOSAGE

Cases of overdose (up to 2 times the recommended dose) have been reported during post-marketing surveillance. Adverse events reported following overdose were similar to those reported with normal vaccine administration.

Contact the Poisons Information Centre on 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

PRIORIX is presented as a whitish to slightly pink powder in a glass vial. The sterile water diluent is clear and colourless and is presented in a glass prefilled syringe or ampoule. The reconstituted vaccine may vary in colour from clear peach to fuchsia pink, without deterioration of the vaccine potency.

The vials and prefilled syringes are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.

The vaccine should be stored between 2°C and 8°C in a refrigerator.

The shelf life of PRIORIX is 24 months from the date of manufacture when stored at a temperature between 2°C and 8°C.

MANUFACTURER

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