

AUSTRALIAN PRODUCT INFORMATION

PRIORIX TETRA (measles, mumps, rubella and varicella) vaccine, (live, attenuated), powder and diluent for solution for injection

1 NAME OF THE MEDICINE

Measles virus, mumps virus, rubella virus and live varicella vaccine.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PRIORIX-TETRA 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), the Wistar RA 27/3 rubella virus strain and the OKA strain of varicella-zoster virus. Each virus strain is separately produced in either chick embryo cells (mumps and measles) or MRC5 human diploid cells (rubella and varicella).

Each 0.5 mL dose of the reconstituted vaccine contains not less than $10^{3.0}$ CCID₅₀ (cell culture infective dose 50%) of the Schwarz measles, not less than $10^{4.4}$ CCID₅₀ of the RIT 4385 mumps, not less than $10^{3.0}$ CCID₅₀ of the Wistar RA 27/3 rubella and not less than $10^{3.3}$ plaque-forming units (PFU) of the varicella-zoster OKA virus strains. The four virus strains are mixed prior to lyophilisation.

The manufacture of this product includes exposure to bovine derived materials sourced to minimise the risk of prion contamination. 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-TETRA meets the World Health Organisation requirements for manufacture of biological substances and for measles, mumps, rubella and varicella vaccines and combined vaccines (live).

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Powder and diluent for solution for injection.

PRIORIX-TETRA is presented as a whitish to slightly pink powder for reconstitution with clear and colourless sterile Water for Injection diluent. The colour of the reconstituted vaccine may vary from clear peach to fuchsia pink.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PRIORIX-TETRA is indicated for active immunisation against measles, mumps, rubella and varicella from 9 months of age.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage (dose and interval)

Infants and children aged from 9 months to 12 years should receive two doses of PRIORIX-TETRA. The dose interval should preferably be between 6 weeks to 3 months. As with other live viral vaccines, in no circumstances should this interval be less than 4 weeks.

Alternatively, and in accordance with applicable official recommendations:

- A single dose of PRIORIX-TETRA may be administered to children who have already received a single dose of another measles, mumps and rubella (MMR) vaccine with or without a single dose of another varicella vaccine.
- A single dose of PRIORIX-TETRA may be administered followed by a single dose of another measles, mumps and rubella (MMR) vaccine with or without a single dose of another varicella vaccine.

Further guidance regarding the use of vaccines is found in the Australian Immunisation Handbook.

There is currently no clinical data available for the use of PRIORIX-TETRA in adolescents or adults.

Method of administration

PRIORIX-TETRA is administered by subcutaneous (SC) or intramuscular (IM) injection. THE VACCINE SHOULD NEVER BE ADMINISTERED INTRAVASCULARLY OR INTRADERMALLY.

The Australian Immunisation Handbook recommends that MMR vaccines should be administered into the anterolateral thigh of children under 12 months of age. The deltoid region is the site of vaccination in children 12 months of age and older.

The vaccine should be administered subcutaneously in children with bleeding disorders (e.g. thrombocytopenia or any coagulation disorder).

Reconstitution

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, the vaccine should be discarded.

The colour of the reconstituted vaccine may vary from clear peach to fuchsia pink due to minor variations of its pH. This is normal and does not impair the performance of the vaccine. In the event of another variation being observed, discard the vaccine.

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. Contains no antimicrobial agent. Product is for single use in one patient only.

Any unused product or waste material should be disposed of in accordance with local requirements.

Instructions for reconstitution of the vaccine with diluent presented in ampoules

PRIORIX-TETRA is reconstituted by adding the entire content of the supplied ampoule of diluent to the vial containing the powder. After the addition of the diluent to the powder, the mixture should be well shaken until the powder is completely dissolved in the diluent.

After reconstitution, the vaccine should be used promptly.

A new needle should be used to administer the vaccine.

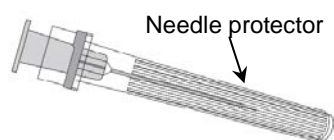
Withdraw the entire contents of the vial.

Instructions for reconstitution of the vaccine with diluent presented in pre-filled syringe

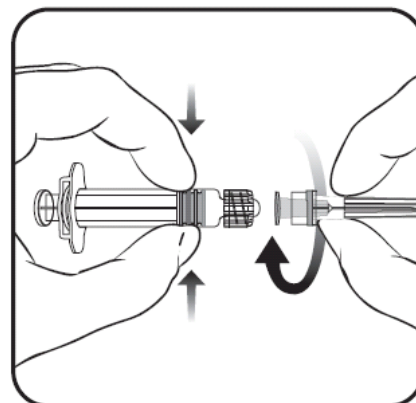
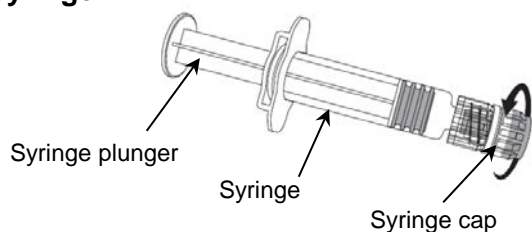
PRIORIX-TETRA must be reconstituted by adding the entire content of the pre-filled syringe of diluent to the vial containing the powder.

To attach a needle to the syringe, refer to the below drawing. However, the syringe provided with PRIORIX-TETRA might be slightly different than the syringe described in the drawing.

Needle



Syringe



1. Holding the syringe **barrel** in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.
2. To attach a needle to the syringe, twist the needle clockwise into the syringe until you feel it lock. (see picture)
3. Remove the needle protector, which on occasion can be a little stiff.

Add the diluent to the powder. After the addition of the diluent to the powder, the mixture should be well shaken until the powder is completely dissolved in the diluent.

After reconstitution, the vaccine should be used promptly.

A new needle should be used to administer the vaccine.

Withdraw the entire contents of the vial.

4.3 CONTRAINDICATIONS

PRIORIX-TETRA is contraindicated in pregnant women. If vaccination of postpubertal women occurs, pregnancy should be avoided for one month (See Section 4.6 FERTILITY, PREGNANCY AND LACTATION, Use in Pregnancy).

PRIORIX-TETRA is contraindicated in children and adults with known hypersensitivity to neomycin or to any other component of the vaccine (for egg allergy, see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). A history of contact dermatitis to neomycin is not a contraindication.

PRIORIX-TETRA is contraindicated in children and adults having shown signs of hypersensitivity after previous administration of measles, mumps, rubella and/or varicella vaccines.

PRIORIX-TETRA is contraindicated in patients with severe humoral or cellular (primary or acquired) immunodeficiency e.g. those receiving high dose steroids (further guidance is found in the Australian Immunisation Handbook) (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with other vaccines, the administration of PRIORIX-TETRA should be postponed in children and adults suffering from acute severe febrile illness ($T > 38.5^{\circ}\text{C}$). However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

PRIORIX-TETRA must not be administered intravascularly or intradermally.

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.

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

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

Limited protection against measles or varicella may be obtained by vaccination up to 72 hours after exposure to natural disease.

Infants in their first year of life may not respond sufficiently to the measles component of the vaccine due to the possible persistence of maternal measles antibodies. Additional doses of a measles containing vaccine should be given according to official recommendations.

The antibody response to the rubella and mumps components is too slow for effective post-exposure prophylaxis.

Transmission of measles, mumps and rubella viruses from vaccinees to susceptible contacts has never been documented, although pharyngeal excretion of the rubella vaccine virus is known to occur about 7 to 28 days after vaccination with peak excretion around the 11th day. Transmission of the Oka vaccine virus has been shown to occur at a very low rate in seronegative contacts of vaccinees with rash. Transmission of the Oka vaccine from a vaccinee who does not develop a rash to seronegative contacts cannot be excluded. Vaccine recipients should attempt to avoid contact for up to 6 weeks, where possible, with immunocompromised individuals who are susceptible to varicella.

Febrile Convulsions

There is an increased risk of fever and febrile convulsions 5 to 12 days after PRIORIX-TETRA when used as the first measles-containing vaccination, as compared with 2 separate injections of MMR and varicella vaccines (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). There was no indication of an increased risk when used as the second measles-containing vaccination.

Fever rates are usually high after the first dose of measles-containing vaccines. Vaccination of children and adults with a history of febrile convulsions or a family history of convulsions should be considered with caution. Alternative immunisation of these children and adults with separate MMR and varicella vaccines should be considered for the first dose (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). In any case vaccinees should be monitored for fever during the risk period ranging from 5 to 12 days after vaccination.

The measles and mumps components of the vaccine are produced in chick embryo cell culture and may therefore contain traces of egg protein. Vaccination of persons with a history of anaphylactic, anaphylactoid, or other immediate reactions (e.g. generalised urticaria, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion cannot be recommended and should only be considered after careful assessment of the benefits and potential risks of administering PRIORIX-TETRA on an individual basis. Individuals who have experienced anaphylaxis after egg ingestion should be vaccinated with extreme caution, with adequate treatment for anaphylaxis on hand.

Egg allergies other than anaphylactic or anaphylactoid reactions are not considered to constitute an increased risk. Children and adults who have experienced such reactions may be considered for vaccination. 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 and varicella vaccine may not result in seroconversion in 100% of susceptible persons given the vaccine. As for other varicella vaccines, cases of varicella disease have been shown to occur in persons who

have previously received PRIORIX-TETRA. These breakthrough cases are usually mild, with a fewer number of lesions and less fever as compared to cases in unvaccinated individuals.

Cases of worsening of thrombocytopenia and recurrence of thrombocytopenia in children 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-TETRA should be carefully evaluated.

There is limited data on the use of PRIORIX-TETRA in immunocompromised patients, therefore vaccination should be considered with caution and only when, in the opinion of the physician, the benefits outweigh the risks, further guidance is found in the Australian Immunisation Handbook.

Immunocompromised patients who have no contraindication for this vaccination (See 4.3 CONTRAINDICATIONS) may not respond as well as immunocompetent patients, therefore some of these patients may acquire measles, mumps, rubella or varicella despite appropriate vaccine administration. Immunocompromised patients should be monitored carefully for signs of measles, mumps, rubella and varicella.

Very few reports exist on disseminated varicella with internal organ involvement following vaccination with the Oka varicella vaccine strain and these are mainly in immunocompromised patients.

No clinical data are available on the safety, immunogenicity, and efficacy of PRIORIX-TETRA in adolescents and adults.

Use in the elderly

No data available.

Paediatric use

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Clinical studies have demonstrated that PRIORIX-TETRA can be given simultaneously with any of the following monovalent or combination vaccines: hexavalent vaccines (DTPa-HBV-IPV/Hib), diphtheria-tetanus-acellular pertussis vaccine (DTPa), Haemophilus influenzae type b vaccine (Hib), inactivated polio vaccine (IPV), hepatitis B vaccine (HBV), hepatitis A vaccine (HAV), meningococcal serogroup B vaccine (MenB), meningococcal serogroup C conjugate vaccine (MenC), meningococcal serogroups A, C, W-135 and Y conjugate vaccine (MenACWY) and 10-valent pneumococcal conjugate vaccine (PCV).

If PRIORIX-TETRA is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

Data are not available on the concurrent administration of PRIORIX-TETRA with Men CCV or the PRP-OMP type Hib vaccine which are included in the ASVS at 12 months of age.

If PRIORIX-TETRA 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 vaccination since it has been reported that combined measles, mumps and rubella vaccines may cause a temporary depression of tuberculin skin sensitivity. As this anergy may last up to a maximum of 6 weeks, tuberculin testing should not be performed within that period after vaccination to avoid false negative results.

In children and adults who have received human gammaglobulins or a blood transfusion, vaccination should be delayed for at least 3 months because of the possibility of vaccine failure due to passively acquired antibodies.

Salicylates should be avoided for 6 weeks after each vaccination as Reye's Syndrome has been reported following the use of salicylates during natural varicella infection.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

PRIORIX-TETRA has not been evaluated for its potential to impair fertility.

Use in pregnancy

(Pregnancy Category B2)

Pregnant women must not be vaccinated with PRIORIX-TETRA. Pregnancy should be avoided for one month after vaccination. Women who intend to become pregnant should be advised to delay pregnancy (see Section 4.3 CONTRAINDICATIONS).

Adequate human data on the use of PRORIX-TETRA during pregnancy are not available and animal studies on reproductive toxicity have not been conducted.

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 one month after vaccination because rubella vaccine can cause foetal infection. 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Experience

Adverse events which might occur following the use of a combined mumps, measles, rubella and varicella vaccine correspond to those observed after administration of the monovalent vaccines alone or in combination.

PRIORIX-TETRA administered in a 2 dose schedule

In controlled clinical studies, signs and symptoms were actively monitored after administration of the commercial formulation of PRIORIX-TETRA to 2,206 subjects. The following table (Table 1) displays a pooled analysis of the incidence of solicited symptoms reported during the 4 day follow-up after vaccination for pain, redness and swelling, the 15 day follow-up for fever and the 43 day follow-up for rash, after each vaccination dose. It compares PRIORIX-TETRA given in a 2-dose schedule in healthy children in the second year of life, with separate administration of PRIORIX and VARILRIX.

Table1. Analysis of reported incidence of any and grade 3 solicited symptoms from Pooled Studies

Symptom		Dose 1: PRIORIX-TETRA Dose 2: PRIORIX-TETRA			Dose 1: PRIORIX + VARILRIX Dose 2: PRIORIX			p < 0.05		
		N	%	95% CI	n	%	95% CI			
Dose 1										
		N= 2206			N= 574					
Fever	≥ 38.0°C	1349	61.15	59.08	63.19	263	45.82	41.69	49.99	*
	> 39.5°C	247	11.20	9.91	12.59	43	7.49	5.47	9.96	*
	≥ 38.0°C Rel	867	39.30	37.26	41.38	164	28.57	24.91	32.46	*
	> 39.5°C Rel	137	6.21	5.24	7.30	22	3.83	2.42	5.75	
Rash	any	448	20.31	18.65	22.05	94	16.38	13.44	19.66	
	measles/ rubella like	110	4.99	4.12	5.98	27	4.70	3.12	6.77	
	varicella-like	24	1.09	0.70	0.61	2	0.35	0.04	1.25	
Pain	Any	209	9.47	8.28	10.77	50	8.71	6.53	11.32	
	Grade 3	2	0.09	0.01	0.33	0	0.00	0.00	0.64	
Redness	Any	596	27.02	25.17	28.92	157	27.35	23.74	31.20	
	> 20 mm	5	0.23	0.07	0.53	0	0.00	0.00	0.64	
Swelling	Any	186	8.43	7.31	9.67	46	8.01	5.93	10.54	
	> 20 mm	7	0.32	0.13	0.65	0	0.00	0.00	0.64	
Dose 2										
		N= 2173			N= 565					
Fever	≥ 38.0°C	636	29.27	27.36	31.23	179	31.68	27.86	35.69	
	> 39.5°C	68	3.13	2.44	3.95	21	3.72	2.32	5.63	
	≥ 38.0°C Rel	351	16.15	14.63	17.77	85	15.04	12.20	18.26	
	> 39.5°C Rel	36	1.66	1.16	2.29	9	1.59	0.73	3.00	
Rash	any	249	11.46	10.15	12.87	59	10.44	8.04	13.26	
	measles/ rubella like	23	1.06	0.67	1.58	9	1.59	0.73	3.00	
	varicella-like	11	0.51	0.25	0.90	0	0.00	0.00	0.65	
Pain	Any	222	10.22	8.97	11.57	26	4.60	3.03	6.67	*
	Grade 3	0	0.00	0.00	0.17	0	0.00	0.00	0.65	
Redness	Any	674	31.02	29.08	33.01	111	19.65	16.45	23.17	*
	> 20 mm	73	3.36	2.64	4.21	1	0.18	0.00	0.98	*
Swelling	Any	267	12.29	10.94	13.74	36	6.37	4.50	8.71	*
	> 20 mm	20	0.92	0.56	1.42	0	0.00	0.00	0.65	

Any: local symptom of "any" intensity

Grade 3 pain = subject cried when limb was moved, spontaneously painful

N = number of subjects having received the considered dose

n/% = number/percentage of subjects reporting the specified symptom

95% CI = Exact 95% confidence interval

LL/UL = Lower Limit/Upper Limit of 95% CI

An asterisk (*) indicates significant differences (p<0.05 using two-sided Wald test) between PRIORIX-TETRA and PRIORIX and VARILRIX/PRIORIX regimens

Rel = Vaccine-related fever

Analysis of the three pivotal studies has shown that redness was the most frequently reported solicited local symptom, in both vaccine treatments. There was no difference between the vaccination regimens, after the first dose.

After the second dose, redness was significantly more frequent in the children who received PRIORIX-TETRA with respect to those who received PRIORIX. No differences in the incidences of pain or swelling between groups were seen after the first dose, however, like redness, both were seen significantly more frequently in children given PRIORIX-TETRA vaccine, after the second dose.

The observed incidence of fever during the first 15-day follow-up period was higher in the pooled PRIORIX-TETRA group as compared to the PRIORIX and VARILRIX group. Differences between groups were statistically significant for fever of any intensity ($\geq 38.0^{\circ}\text{C}$) and for Grade 3 fever ($>39.5^{\circ}\text{C}$). After the second dose, no differences in fever symptoms were observed in between the two vaccine groups. The use of antipyretics might be considered after vaccination.

For rash, no statistically significant differences were observed between vaccine groups for either the first or the second dose.

Other events

Other unsolicited events reported in clinical trials for PRIORIX-TETRA are listed below. Causality has not formally been established. The safety profile presented below is based on data from more than 6,700 doses administered subcutaneously to children from 9 to 27 months of age. Events were recorded for up to 42 days after vaccination.

Very common events: $\geq 1/10$

Common events: $\geq 1/100$ and $< 1/10$

Uncommon events: $\geq 1/1000$ and $< 1/100$

Rare events: $\geq 1/10000$ and $< 1/1000$

Very rare events: $< 1/10000$

Infections and infestations

Uncommon: upper respiratory tract infection

Rare: otitis media

Blood and lymphatic system disorders

Uncommon: lymphadenopathy

Metabolism and nutrition disorders

Uncommon: anorexia

Psychiatric disorders

Common: irritability

Uncommon: abnormal crying, nervousness, insomnia, somnolence

Nervous system disorders

Rare: febrile convulsions

Respiratory, thoracic and mediastinal disorders

Uncommon: rhinitis

Rare: cough, bronchitis

Gastrointestinal disorders

Uncommon: parotid gland enlargement, diarrhoea, vomiting

Skin and subcutaneous tissue disorders

Common: rash

General disorders and administration site conditions

Very Common: pain and redness at the injection site, fever (rectal $\geq 38^{\circ}\text{C}$ - $\leq 39.5^{\circ}\text{C}$, axillary/oral: $\geq 37.5^{\circ}\text{C}$ - $\leq 39^{\circ}\text{C}$)

Common: swelling at the injection site, fever (rectal $> 39.5^{\circ}\text{C}$, axillary/oral $> 39^{\circ}\text{C}$)

Uncommon: lethargy, malaise, fatigue

PRIORIX-TETRA administered as second dose after a first dose of MMR/V

PRIORIX-TETRA administered as a second dose of MMR vaccine in children 15 months to 6 years of age was evaluated in 2 clinical studies. Children were previously primed with respectively an MMR vaccine (MMR; N=478) or with an MMR vaccine co-administered with a live attenuated varicella vaccine (MMR+V; N=390) and randomised in both studies to receive either PRIORIX-TETRA or PRIORIX and VARILRIX given concomitantly.

In both studies, the incidence of local solicited symptoms (pain, redness and swelling) was reported during the 4 day follow-up after vaccination with PRIORIX-TETRA or PRIORIX and VARILRIX. There was no difference between the vaccination regimens with regards to pain, redness and swelling in the study where children were primed with an MMR vaccine only. In the study where children were primed with an MMR vaccine coadministered with a varicella vaccine exploratory analyses showed a statistically significantly higher incidence of pain with PRIORIX-TETRA (33.3% vs 23.7%; $p=0.043$). The other notable effect, although not statistically significant in the exploratory analysis, is the difference in redness grade 3 ($>20\text{mm}$) which was 14.4% in the PRIORIX-TETRA group as compared to 8.2% in the group receiving PRIORIX and VARILRIX ($p=0.077$).

In both studies, the incidence of fever was reported during the 15 day and 43 day follow-up period after vaccination with PRIORIX-TETRA or PRIORIX and VARILRIX. Rash was reported during the 43 day follow-up period. *An exploratory analysis showed no statistical differences between the vaccination regimens with respect to all fever or grade 3 fever ($>39.5^{\circ}\text{C}$).* Similar incidences of rash were obtained in both groups.

The reported incidence of local solicited symptoms, fever and rash following PRIORIX-TETRA or PRIORIX and VARILRIX administered to children who had previously received a single dose of MMR is provided in Table 2 below.

Table 2: Analysis of reported incidence of any and grade 3 solicited symptoms following PRIORIX-TETRA or PRIORIX and VARILRIX administered to children who had previously received a single dose of MMR

Symptom		PRIORIX-TETRA N = 226			PRIORIX+VARILRIX N = 224		
		n	%	95%CI	n	%	95%CI
Fever (15 day follow-up)	≥38°C	64	28.3	22.5;34.7	58	25.9	20.3;32.1
	>39.5°C	6	2.7	1.0;5.7	6	2.7	1.0;5.7
	>39.5°C related	4	1.8	0.5;4.5	1	0.4	0.0;2.5
Rash generalised (43 day follow-up)	Any	15	6.6	3.8;10.7	16	7.1	4.1;11.3
	Grade 3	2	0.9	0.1;3.2	1	0.4	0.0;2.5
Pain (4 day follow-up)	Any	36	16.0	11.5;21.5	36	16.1	11.5;21.5
	Grade 3	0	0.0	0.0;1.6	1	0.4	0.0;2.5
Redness (4 day follow-up)	Any	53	23.6	18.2;29.7	40	17.9	13.1;23.5
	>20mm	4	1.8	0.5;4.5	3	1.3	0.3;3.9
Swelling (4 day follow-up)	Any	18	8.0	4.8;12.3	19	8.5	5.2;12.9
	>20mm	1	0.4	0.0;2.5	3	1.3	0.3;3.9

Any: local symptom of “any” intensity

Grade 3 pain = subject cried when limb was moved, spontaneously painful

Grade 3 rash = >150 lesions

N = number of subjects having received the considered dose

n/% = number/percentage of subjects reporting the specified symptom

When summarised according to age stratum for toddlers (15 months – 2 years) and children (2 – 6 years) lower levels of all fever were reported in toddlers who received PRIORIX-TETRA as a second dose of a measles containing vaccine post MMR vaccine (40.9%), compared to studies where toddlers were administered PRIORIX-TETRA as a first dose of a measles containing vaccine (61.15%). Fever >39.5°C was observed in 2.7% of toddlers who received PRIORIX-TETRA as a second dose of a measles containing vaccine post MMR vaccine, compared with 11.2% in studies where PRIORIX-TETRA was used as the first dose of a measles containing vaccine.

Post-marketing data

During post-marketing surveillance, the following reactions have been reported additionally in temporal association with measles, mumps, rubella and varicella vaccination:

Infections and infestations

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

Blood and lymphatic system disorders

Rare: thrombocytopenia, thrombocytopenic purpura

Immune system disorders

Rare: allergic reactions (including anaphylactic and anaphylactoid reactions)

Nervous system disorders

Rare: encephalitis, cerebrovascular accident, 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, varicella like rash

Musculoskeletal and connective tissue disorders

Rare: arthralgia, arthritis

Febrile convulsions

The risk of febrile convulsions in children aged 9 to 30 months following PRIORIX-TETRA given as the first measles containing vaccine compared with a matched cohort who received either MMR or concomitant MMR and varicella vaccination was assessed in a retrospective database analysis.

The study included 82,656 children immunized with PRIORIX-TETRA, 149,259 with MMR and 39,203 with separate MMR and varicella vaccines. The attributable risk of febrile convulsions in the main risk period of 5 to 12 days following PRIORIX-TETRA was 3.64/10,000 (95% CI: -6.11; 8.30), corresponding to 1 additional case of febrile convulsions per 2,747 subjects receiving PRIORIX-TETRA as the first dose of measles-containing vaccination compared to MMR or concomitant MMR and varicella vaccination.

In the 0 to 30 day time period following vaccination the attributable risk was 3.88/10,000 (95% CI: -14.25;15.93), corresponding to 1 additional case of febrile convulsions per 2,577 subjects receiving PRIORIX-TETRA. When used as the second measles-containing vaccination, there is no indication of an increased risk.

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.

4.9 OVERDOSE

Insufficient data are available.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

PRIORIX-TETRA induces protective antibodies against all four viruses.

Clinical trials

Immunogenicity Studies

Immunogenicity data of PRIORIX-TETRA has not been studied in subjects above 6 years of age, but PRIORIX-TETRA may be used in subjects up to 12 years of age based on previous experience with the separate component vaccines, PRIORIX and VARILRIX.

PRIORIX-TETRA administered in a 2 dose schedule

The immunogenicity with the commercial formulation of PRIORIX-TETRA has been established in randomised controlled clinical trials comparing PRIORIX-TETRA with separate injections of measles, mumps and rubella (PRIORIX) and varicella (VARILRIX) vaccines in subjects aged 11 to 23 months. Approximately 2,000 subjects randomised to receive two subcutaneous doses of PRIORIX-TETRA given six weeks apart, were compared to approximately 500 subjects randomised to receive two doses of PRIORIX six weeks apart and one dose of VARILRIX at the time of first vaccination. Seroconversion data were collected 42 days following each vaccination.

Table 3. Seroconversion Rates 42 Days Post-Vaccination (According to Protocol Immunogenicity Cohort) – Pooled Studies

Antibody	Dose 1: PRIORIX-TETRA Dose 2: PRIORIX-TETRA			Dose 1: PRIORIX + VARILRIX Dose 2: PRIORIX		
	N	%	95% CI	N	%	95% CI
DOSE 1						
Measles (ELISA)	2019	96.4	95.5–97.2	509	95.5	93.3-97.1
Mumps (ELISA)	1963	91.3	90.0-92.5	495	93.9	91.5-95.9
Mumps (PRNT)	1741	95.4	94.3-96.3	444	96.8	94.8-99.7
Rubella (ELISA)	2022	99.7	99.4-99.9	507	99.2	98.0-99.8
Varicella (IFA)	1934	97.2	96.3-97.9	494	96.6	94.5-98.0
Varicella (ELISA)	1566	89.4	87.8-90.8	374	86.8	83.2-89.8
DOSE 2						
Measles (ELISA)	1987	99.1	98.6-99.5	505	98.4	96.9-99.3
Mumps (ELISA)	1982	98.8	98.2-99.2	501	99.4	98.3-99.9
Mumps (PRNT)	1709	99.4	98.9-99.7	440	99.5	98.4-99.9
Rubella (ELISA)	1989	99.9	99.6-100.0	504	100.0	99.3-100.0
Varicella (IFA)	1908	99.8	99.5-100.0	489	98.0	96.3-99.0
Varicella (ELISA)	1307	99.2	98.5-99.6	225	76.8	71.5-81.5

N= Number of subjects in cohort.

ELISA = Enzyme linked immunosorbent assay of antigen-specific IgG. Anti-measles ELISA \geq 150 mIU/mL assay cut-off; Anti-mumps ELISA \geq 231 U/mL assay cut-off; Anti-rubella ELISA \geq 4 IU/mL assay cut-off.

PRNT = Plaque reduction neutralisation assay. \geq 28 ED₅₀ assay cut-off. ED₅₀ assay = Endpoint Dilution 50% or more i.e. Highest serum dilution reducing the number of viral plaques by 50%.

IFA = Immunofluorescence assay. \geq 4 Dilution⁻¹ assay cut-off.

Three years after vaccination with two doses of PRIORIX-TETRA, 98.5%, 97.4%, 100% and 99.4% of all vaccinees were still seropositive for respectively anti-measles, anti-mumps, anti-rubella and anti-varicella antibodies.

In a study with an earlier formulation of the GSK MMRV combination vaccine (with a reduced mumps content) a total of 300 healthy infants aged 9 to 10 months, without previous history

of varicella were administered either 2 doses of GSK MMRV combination vaccine or 2 doses of PRIORIX and VARILRIX. Doses were administered with an interval of 3 months. All subjects were seropositive for all four vaccine antigens after two doses of this predecessor formulation of PRIORIX-TETRA. After a first dose seroconversion rates were comparable for all antigens to those seen in 12-24 months old children in other clinical studies except as expected mumps and a lower trend for measles. After the second dose of these respective vaccines all subjects had seroconverted, with anti-rubella GMTs similar in both groups and anti-measles, anti-mumps and anti-varicella GMTs higher in the predecessor formulation of PRIORIX-TETRA group compared to PRIORIX +VARILRIX.

PRIORIX-TETRA administered as second dose after a first dose of MMR/V

PRIORIX-TETRA administered as a second dose of MMR vaccine in children 15 months to 6 years of age was evaluated in 2 clinical studies. Children were previously primed with respectively an MMR vaccine (N=458) or with an MMR vaccine co-administered with a live attenuated varicella vaccine (N=390) and randomised to receive either PRIORIX-TETRA or PRIORIX and VARILRIX given concomitantly.

Seropositivity rates after administration of PRIORIX-TETRA for anti-varicella antibodies were 97.9% (IFA) in children [between 15 months and 6 years of age] previously vaccinated with MMR and 100% in children previously vaccinated with an MMR vaccine co-administered with a live attenuated varicella vaccine. Seropositivity rates were at least 99.5% for anti-measles, mumps and rubella antibodies in both studies. Immune responses in terms of GMTs for measles, mumps, rubella and varicella obtained with PRIORIX-TETRA were comparable with the immune responses obtained with PRIORIX and VARILRIX administered as separate injections

Efficacy studies

In clinical studies it has been shown that the vast majority of subjects who receive varicella vaccines and are exposed to wild-type virus are either completely protected from chickenpox or develop a milder form of the disease (breakthrough varicella).

The efficacy of GlaxoSmithKline (GSK)'s OKA/RIT varicella vaccines in preventing confirmed varicella disease (varicella cases were confirmed by polymerase chain reaction {PCR} or exposure to a varicella case) has been evaluated in a large active controlled clinical trial in which children aged 12-22 months received two doses of PRIORIX-TETRA (N = 2279), given six weeks apart, or one dose of VARILRIX (N = 2263). The co-primary objective to demonstrate vaccine efficacy with PRIORIX-TETRA on a two dose schedule was met. The co-primary objective of this trial with respect to VARILRIX was to demonstrate vaccine efficacy of $\geq 60\%$ in comparison to PRIORIX. The efficacy of VARILRIX (one dose) versus PRIORIX in respect of preventing confirmed varicella cases was 65.4% (97.5% CI: 57.2-72.1%), the lower limit of the 2-sided 97.5% CI however did not exceed the pre-defined criterion of 60%. The observed vaccine efficacy against confirmed varicella of any severity and against moderate or severe confirmed varicella after 2 doses of PRIORIX-TETRA and after one dose of VARILRIX (mean follow-up period 35 months) are presented in Table 4.

Table 4: Efficacy results after 2 doses of PRIORIX-TETRA compared to one dose of VARILRIX

Group	N	n	Vaccine Efficacy 97.5%CI
Efficacy against confirmed Varicella of any Severity			
PRIORIX-TETRA	2279	37	94.9% 92.4 – 96.6
VARILRIX	2263	243	65.4% 57.2 – 72.1
Efficacy against confirmed Moderate or Severe Varicella			
PRIORIX-TETRA	2279	2	99.5% 97.5 – 99.9
VARILRIX	2263	37	90.7% 85.9 – 93.9

N= Number of subjects included in each group

n = Number of subjects reporting at least one event(s) in each group

In a pivotal clinical study in subjects receiving two-doses of PRIORIX-TETRA given six weeks apart, at the one year follow-up after the second dose of PRIORIX-TETRA, no breakthrough cases were reported for measles, mumps and rubella despite reported contacts with wild virus. Exposures to varicella or zoster were reported in 14.5% in the PRIORIX-TETRA group versus 20.0% in the control group (PRIORIX + VARILRIX for the first dose; PRIORIX alone for the second dose). Breakthrough cases were reported in 0.34% of PRIORIX-TETRA recipients, as opposed to 1.9% of children in the control group.

After 3 years follow-up of the same study, lower incidences of varicella breakthrough cases were reported in the group receiving two-doses of PRIORIX-TETRA (1 case, 0.44%) than in the group receiving only one dose of VARILRIX (4 cases, 5.06%), however the number of breakthrough cases were too small to make any conclusion about comparative vaccine efficacy. No cases of measles, mumps or rubella breakthrough disease were reported in any group during this 3 years follow-up.

In a study specifically designed to evaluate vaccine efficacy with VARILRIX, which contains the same active ingredient as PRIORIX-TETRA, 493 children aged 10 to 30 months old were followed up for a period of 29.3 months. The protective efficacy was 100% against common clinical cases of varicella and 88% against any cases.

The immunogenicity and safety of PRIORIX-TETRA administered intramuscularly was evaluated in one comparative study conducted in 328 children who received PRIORIX-TETRA either by intramuscular or subcutaneous route. The study demonstrated similar immunogenicity and safety profiles for both administration routes.

Effectiveness studies

Effectiveness data from an outbreak investigation suggest a higher level of protection and a decrease in breakthrough varicella (not statistically significant) following two doses of varicella-containing vaccine than following one dose. The effectiveness of two doses of

PRIORIX-TETRA was 91% (95% CI: 65-98%) against any disease and 94% (95% CI: 54-99%) against moderate disease.

5.2 PHARMACOKINETIC PROPERTIES

Not relevant to vaccines.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

PRIORIX-TETRA has not been evaluated for carcinogenicity or mutagenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The lyophilised vaccine also contains lactose monohydrate, amino acids and sorbitol and mannitol as stabilisers. Neomycin sulphate is present as a residual from the manufacturing process. There is no human serum albumin in PRIORIX-TETRA.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

The vaccine should be stored between 2°C and 8°C in a refrigerator. Store in the original packaging in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

PRIORIX-TETRA 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 colour of the reconstituted vaccine may vary from clear peach to fuchsia pink due to minor variations of its pH. This is normal and does not impair the performance of the vaccine. In the event of another variation being observed, discard the vaccine.

PRIORIX-TETRA is available in pack sizes of 1 or 10.

Not all pack sizes and container types may be distributed in Australia.

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

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Not relevant to vaccines.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformat
4.2	Reorganisation of information on reconstitution, and addition of instructions for reconstitution with new syringe type
6.5	Addition of pack sizes

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