PRIORIX-TETRA® PRODUCT INFORMATION

Measles, mumps, rubella and varicella vaccine (live, attenuated)

NAME OF THE DRUG

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

DESCRIPTION

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).

PRIORIX-TETRA is presented as a white to slightly pink pellet for reconstitution with sterile Water for Injection diluent.

Each 0.5mL dose of the reconstituted vaccine contains not less than $10^{3.0}$ $CCID_{50}$ (cell culture infective dose 50%) of the Schwarz measles, not less than $10^{4.4}$ $CCID_{50}$ of the RIT 4385 mumps, not less than $10^{3.0}$ $CCID_{50}$ 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 lyophilised vaccine also contains lactose, neomycin sulfate, amino acids and sorbitol and mannitol as stabilisers. There is no human serum albumin in *PRIORIX-TETRA.*

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).

PHARMACOLOGY

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 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 1. 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 ≥ 150 mIU/mL assay cut-off; Anti-mumps ELISA ≥ 231 U/mL assay cut-off; Anti-rubella ELISA ≥ 4 IU/mL assay cut-off.
PRNT = Plaque reduction neutralisation assay. ≥ 28 ED_{50} assay cut-off. ED_{50} assay = Endpoint Dilution 50% or more i.e. Highest serum dilution reducing the number of viral plaques by 50%.
IFA = Immunofluorescence assay. ≥ 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 *PRIORIX-TETRA* 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 *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 ≥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 2.

Table 2: 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.

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.

INDICATIONS

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

CONTRAINDICATIONS

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

PRIORIX-TETRA is contraindicated in subjects with known hypersensitivity to neomycin or to any other component of the vaccine (for egg allergy, see *Precautions*). A history of contact dermatitis to neomycin is not a contraindication.

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

PRIORIX-TETRA should not be given to subjects with impaired immune function. 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).

PRECAUTIONS

As with other vaccines, the administration of *PRIORIX-TETRA* should be postponed in subjects suffering from acute severe febrile illness (T>38.5ºC). However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

***PRIORIX-TETRA* should under no circumstances 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.

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. 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*).

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. Post-marketing experience suggests that transmission of varicella vaccine virus may occur very rarely between healthy vaccinees who develop a varicella-like rash and healthy susceptible contacts. Vaccine recipients should attempt to avoid contact for up to 6 weeks, where possible, with immunocompromised individuals who are susceptible to varicella.

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 “Adverse Reactions”). 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 subjects with a history of febrile convulsions or a family history of convulsions should be considered with caution. Alternative immunisation of these subjects with separate MMR and varicella vaccines should be considered for the first dose (see ‘DOSAGE AND 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 can not 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 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.

Cases of worsening of 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-Tetra should be carefully evaluated.

The use of *PRIORIX-TETRA* in asymptomatic HIV subjects has not been studied. Administration of *PRIORIX-TETRA* may be considered with caution in this population when, in the opinion of the physician, withholding the vaccine entails a greater risk.

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

Carcinogenicity and Mutagenicity

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

Impairment of Fertility

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

Use in Pregnancy (Category B2):

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

The Australian Medicines in Pregnancy handbook (4th 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 NHMRC 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

PRIORIX-TETRA can be given simultaneously with monovalent or combination vaccines containing diphtheria (D), tetanus (T), acellular pertussis (Pa), hepatitis B (HBV), inactivated poliovirus (IPV) and *Haemophilus influenzae* type b (Hib), taking into account generally accepted vaccine practices and recommendations, for example, injectable vaccines should always be given at different 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 subjects 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.

ADVERSE 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 3) 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*.

Table3. Analysis of reported incidence of any and grade 3 solicited symptoms from Pooled Studies

		Dose 1: Priorix-Tetra Dose 2: Priorix-Tetra				Dose 1: Priorix + Varilrix Dose 2: Priorix				p < 0.05
Symptom		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 (≥38.0˚C) and for Grade 3 fever (>39.5˚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 to children from 9 to 27 months of age. Events were recorded for up to 42 days after vaccination.

Very common events: *≥1/10*
Common events: *≥1/100 and <1/10*

Uncommon events: *≥1/1000 and <1/100*
Rare events: *≥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
Endocrine disorders: *Uncommon:* parotid swelling
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:* 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 ≥38˚C - ≤39.5˚C, axillary/oral: ≥37.5˚C - ≤39˚C); *Common:* swelling at the injection site, fever (rectal >39.5˚C, axillary/oral >39˚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=0043). The other notable effect, although not statistically significant in the exploratory analysis, is the difference in redness grade 3 (>20mm) 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 (>39.5ºC). 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 4 below.

Table 4: 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

		Priorix-Tetra N = 226			**Priorix+Varilrix N = 224**		
Symptom		**n**	**%**	**95%CI**	**n**	**%**	**95%CI**
Fever (15 day follow-up)	≥38ºC	64	28.3	22.5;34.7	58	25.9	20.3;32.1
	>39.5ºC	6	2.7	1.0;5.7	6	2.7	1.0;5.7
	>39.5ºC 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 >39.5ºC 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: *Very rare:* meningitis, orchitis, epididymitis, mumps-like syndrome
Blood and lymphatic system disorders: *Very rare:* thrombocytopenia, thrombocytopenic purpura
Immune system disorders: *Very rare:* allergic reactions (including anaphylactic and anaphylactoid reactions)
Nervous system disorders: *Very rare:* encephalitis, cerebrovascular accident, cerebellitis, cerebellitis like symptoms, Guillain Barré syndrome, transverse myelitis, peripheral neuritis,
Skin and subcutaneous tissue disorders: *Very rare:* erythema multiforme
Musculoskeletal and connective tissue disorders: *Very rare:* arthralgia, arthritis
General disorders and administration site conditions: *Very rare:* Kawasaki syndrome

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. In the event of either being observed, the vaccine should be discarded.

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

Dosage

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

Subjects 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.

Administration

PRIORIX-TETRA is administered by subcutaneous injection. THE VACCINE SHOULD NEVER BE ADMINISTERED INTRAVASCULARLY OR INTRADERMALLY.

The NHMRC 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 subjects 12 months of age and older.

In accordance with NHMRC guidelines, protection against measles may be obtained by vaccination of children up to and including 12 years of age within 72 hours after exposure to natural measles. Effective protection against varicella is usually obtained by vaccination within 3 days, and up to 5 days after exposure to wild varicella virus. If the vaccination status of the subject is in doubt, the vaccine should be given as there are no ill effects of vaccinating individuals who are already immune to any of the antigens in PRIORIX-TETRA.

OVERDOSAGE

Insufficient data are available.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATIONS AND STORAGE CONDITIONS

PRIORIX-TETRA is presented as a whitish to slightly pink pellet 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.

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. Store in the original packaging in order to protect from light.

The expiry date of the vaccine is indicated on the label and packaging. The shelf life of *PRIORIX-TETRA* is 18 months from the date of manufacture when stored at a temperature between +2°C and +8°C.

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

MANUFACTURER:

GlaxoSmithKline Biologicals SA
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NAME AND ADDRESS OF THE SPONSOR

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Auckland NZ

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PRIORIX-TETRA® is a registered trademark of the GlaxoSmithKline group of companies.

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