

Priorix-Tetra™

1. NAME OF THE MEDICAL PRODUCT

Priorix-Tetra™

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.5 ml) contains:

Live attenuated measles virus ¹ (Schwarz strain)	not less than 10 ^{3.0} CCID ₅₀ ³
Live attenuated mumps virus ¹ (RIT 4385 strain, derived from Jeryl Lynn strain)	not less than 10 ^{4.4} CCID ₅₀ ³
Live attenuated rubella virus ² (Wistar RA 27/3 strain)	not less than 10 ^{3.0} CCID ₅₀ ³
Live attenuated varicella virus ² (OKA strain)	not less than 10 ^{3.3} PFU ⁴

¹ produced in chick embryo cells

² produced in human diploid (MRC-5) cells

³ Cell Culture Infective Dose 50%

⁴ Plaque forming units

The powder is white to slightly pink.

The solvent is clear and colourless.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Priorix-Tetra™ is indicated for active immunisation in subjects from the age of 9 months up to 12 years of age inclusive against measles, mumps, rubella and varicella. (see also 4.4 Special Warnings and Precautions for Use).

4.2 Posology and Method of Administration

Posology

Subjects from the age of 9 months up to and including 12 years of age should receive 2 doses of **Priorix-Tetra™** to ensure optimal protection against measles, mumps, rubella and varicella (see 5.1 Pharmacodynamic Properties).

It is preferable to respect an interval of at least 6 weeks between doses. 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 and/or 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 and/or a single dose of another varicella vaccine.

* Applicable official recommendations may vary regarding the interval between doses and the need for one or two doses of measles, mumps and rubella and of varicella-containing vaccines.

Method of administration

The vaccine is to be injected subcutaneously (SC) or intramuscularly (IM) in the deltoid region or in the anterolateral area of the thigh.

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

For instructions on reconstitution of the medicinal product before administration see 6.6 Instructions for Use and Handling.

4.3 Contra-indications

Priorix-Tetra™ is contraindicated in subjects with known hypersensitivity to neomycin or to any other component of the vaccine (for egg allergy, see 4.4 Special Warnings and Precautions for Use). 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™ is contra-indicated in pregnant women. Pregnancy should be avoided for one month after vaccination (see 4.6 Pregnancy and Lactation).

Priorix-Tetra™ is contraindicated in subjects with severe humoral or cellular (primary or acquired) immunodeficiency (see also 4.4 Special Warnings and Precautions for Use).

4.4 Special Warnings and Special Precautions for Use

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

As with other vaccines, the administration of **Priorix-Tetra™** should be postponed in subjects suffering from acute severe febrile illness. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

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 since 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.

There is an increased risk of fever and febrile convulsions 5 to 12 days after the first dose of **Priorix-Tetra™** as compared with 2 separate injections of MMR and varicella vaccines (see 4.8 Undesirable Effects and 5.1 Pharmacodynamic Properties). There was no indication of an increased risk after the second dose.

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 4.2 Posology and

method of administration). In any case, vaccinees should be monitored for fever during the risk period.

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. generalised urticaria, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion may be at an enhanced risk of immediate-type hypersensitivity reactions after vaccination, although these types of reactions have been shown to be very rare. Individuals who have experienced anaphylaxis after egg ingestion should be vaccinated with extreme caution, with adequate treatment for anaphylaxis on hand should such a reaction occur.

Transmission of measles, mumps and rubella viruses from vaccinees to susceptible contacts has never been documented, although pharyngeal excretion of the rubella 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.

Priorix-Tetra™ must not be administered intravascularly or intradermally.

As with any vaccine, a protective immune response may not be elicited in all vaccinees. 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 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.

There is limited data on the use of **Priorix-Tetra™** in immunocompromised subjects, therefore vaccination should be considered with caution and only when, in the opinion of the physician, the benefits outweigh the risks.

Immunocompromised subjects who have no contraindication for this vaccination (see 4.3 Contraindications) may not respond as well as immunocompetent subjects, therefore some of these subjects may acquire measles, mumps, rubella or varicella despite appropriate vaccine administration. Immunocompromised subjects 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 Oka varicella vaccine strain mainly in immunocompromised subjects.

4.5 Interaction with Other Medical Products and Forms of Interactions

Clinical studies have demonstrated that **Priorix-Tetra™** can be given simultaneously with any of the following monovalent or combination vaccines [including 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 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.

If tuberculin testing has to be done 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 three months because of the likelihood 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.

4.6 Use During Pregnancy and Lactation

Fertility

No data available.

Use in Pregnancy

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.

Adequate human data on the use of **Priorix-Tetra™** during pregnancy are not available and animal studies on reproductive toxicity have not been conducted.

Use in Lactation

Adequate human data on the use of **Priorix-Tetra™** during lactation are not available.

4.7 Effects on the Ability to Drive and Use Machines

Not relevant.

4.8 Undesirable Effects

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.

Frequencies are reported as:

Very common ($\geq 1/10$)/

Common ($\geq 1/100$ to $<1/10$)/

Uncommon ($\geq 1/1,000$ to $<1/100$)/

Rare ($\geq 1/10,000$ to $<1/1,000$)/

Very rare ($<1/10,000$)

System Organ Class	Frequency	Adverse reactions
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	crying, nervousness, insomnia
Nervous system disorders	Rare	febrile convulsions
Respiratory, thoracic and	Uncommon	rhinitis

mediastinal disorders	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

*Following the administration of the first dose of the combined measles-mumps-rubella-varicella vaccine, higher incidences of fever (approximately 1.5 fold) were observed when compared to the concomitant administration of measles-mumps-rubella and varicella vaccines at separate injection sites.

During post-marketing surveillance, the following additional reactions have been reported after measles-mumps-rubella and varicella vaccination:

System Organ Class	Frequency	Adverse reactions
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

4.9 Overdose

Insufficient data are available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Efficacy and effectiveness

Clinical trials showed that the vast majority of varicella vaccinees exposed to wild-type virus were either completely protected or developed a milder form of chickenpox (breakthrough varicella).

The efficacy of GlaxoSmithKline's Oka/RIT varicella vaccines in preventing confirmed varicella disease (by Polymerase Chain reaction (PCR) or exposure to varicella case) was evaluated in a large active controlled clinical trial in which children aged 12-22 months received two doses of **Priorix-Tetra**TM or one dose of monovalent Oka/RIT vaccine. Vaccine efficacy against

confirmed varicella of any severity and against moderate or severe confirmed varicella observed after a primary follow-up period of 2 years (median duration 3.2 years) and after an extended follow-up period of 6 years (median duration 6.4 years) are presented in the Table below.

Group	Timing	Efficacy against confirmed varicella of any severity	Efficacy against moderate or severe confirmed varicella
Priorix-Tetra™ (2 doses) N = 2,489	Year 2	94.9% (97.5% CI: 92.4;96.6)	99.5% (97.5% CI: 97.5;99.9)
	Year 6 ⁽¹⁾	95.0% (95% CI: 93.6;96.2)	99.0% (95% CI: 97.7;99.6)
Monovalent Oka/RIT vaccine (1 dose) N = 2,487	Year 2	65.4 % (97.5% CI: 57.2;72.1)	90.7% (97.5% CI: 85.9;93.9)
	Year 6 ⁽¹⁾	67.0% (95% CI: 61.8;71.4)	90.3% (95% CI: 86.9;92.8)

N = number of subjects enrolled and vaccinated

(1) descriptive analysis

Effectiveness data suggest a higher level of protection and a decrease in breakthrough varicella following two doses of varicella-containing vaccine than following one dose.

In an outbreak situation 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.

Immune response

Seroconversion rates after two doses subcutaneous of **Priorix-Tetra™** given with an interval of 6 weeks in approximately 2,000 previously unvaccinated children from 11 to 23 months of age are summarized in the table below:

Antibody Test (cut-off)	Post dose 1	Post dose 2
Measles, ELISA (150 mIU/ml)	96.4%	99.1%
Mumps, ELISA (231 U/ml)	91.3%	98.8%
Neutralisations (1:28)	95.4%	99.4%
Rubella, ELISA (4 IU/ml)	99.7%	99.9%
Varicella, IFA (1:4)	97.2%	99.8%
ELISA (50m IU/ml)	89.4%	99.2%

ELISA: Enzyme Linked Immuno Sorbent Assay

IFA: Immunofluorescence Assay

In children 9 to 10 months of age vaccinated with 2 doses of **Priorix-Tetra™**, seroconversion rates after a first dose of **Priorix-Tetra™** were comparable for all antigens except measles to those seen in 12-24 months old children in other clinical studies.

When **Priorix-Tetra™** administered as a second dose of MMR vaccine in children 24 months to 6 years of age, previously primed with an MMR vaccine or with MMR co-administered with a live attenuated varicella vaccine all children were found seropositive for anti-measles, mumps and rubella antibodies. Seropositivity rates for anti-varicella antibodies were respectively 98.1%

(IFA) and 100% in the children previously vaccinated with MMR or with MMR co-administered with a live attenuated varicella vaccine.

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.

Persistence of measles, mumps and rubella immune response

In a clinical trial in which children aged 12-22 months received two doses of **Priorix-Tetra™** (N = 2,489), the seropositivity rates for anti-measles, mumps and rubella antibodies, in terms of subjects with an antibody concentration equal to or above defined threshold, observed after follow-up periods of 2 years and 6 years are presented in the Table below:

Timing	Antibody Test (cut-off)		
	Measles ELISA (150 mIU/ml)	Mumps ELISA (231 U/ml)	Rubella ELISA (4 IU/ml)
Year 2	99.1%	90.5%	100%
Year 6	99.0%	90.5%	99.8%

ELISA: Enzyme Linked Immuno Sorbent Assay

Post-Marketing Observational Safety Surveillance Study

The risk of febrile convulsions following the first dose vaccination of children aged 9 to 30 months with **Priorix-Tetra™** compared with a matched cohort who received MMR or simultaneous, but separate MMR and varicella vaccination, was assessed in a retrospective database analysis.

The study included 82,656 children immunised with MMRV, 149,259 with MMR and 39,203 with separate MMR and varicella vaccines.

The attributable risk of febrile convulsions on cohorts matched for confounding factors in the main risk period of 5 to 12 days following first dose of **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.

5.2 Pharmacokinetic Properties

Evaluation of pharmacokinetic properties is not required for vaccines.

Clinical Studies

See 5.1 Pharmacodynamic Properties

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Excipients of the vaccine are: amino acids, lactose, mannitol, sorbitol.

Solvent is water for injections.

Neomycin sulphate is present as a residual from the manufacturing process.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf Life

The expiry date of the vaccine is indicated on the label and packaging.

After reconstitution: immediate use is recommended. However the stability at + 2°C to + 8°C has been demonstrated for 8 hours after reconstitution.

6.4 Special Precautions for Storage

Store at 2°C to 8°C (in a refrigerator).

Do not freeze.

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

6.5 Nature and Contents of Container

Powder in a vial (Type I glass) with a stopper.

0.5 ml of solvent in an ampoule (Type I glass)

or

0.5 ml of solvent in a pre-filled syringe (Type I glass) with rubber stopper, with or without needles.

6.6 Instructions for Use/Handling

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 other variation being observed, discard the vaccine.

Instructions for reconstitution of the vaccine with solvent presented in ampoules

Priorix-Tetra™ is reconstituted by adding the entire contents of the supplied ampoule of solvent to the vial containing the powder. After the addition of the solvent to the powder, the mixture should be well shaken until the powder is completely dissolved in the solvent.

After reconstitution, the vaccine should be used promptly.

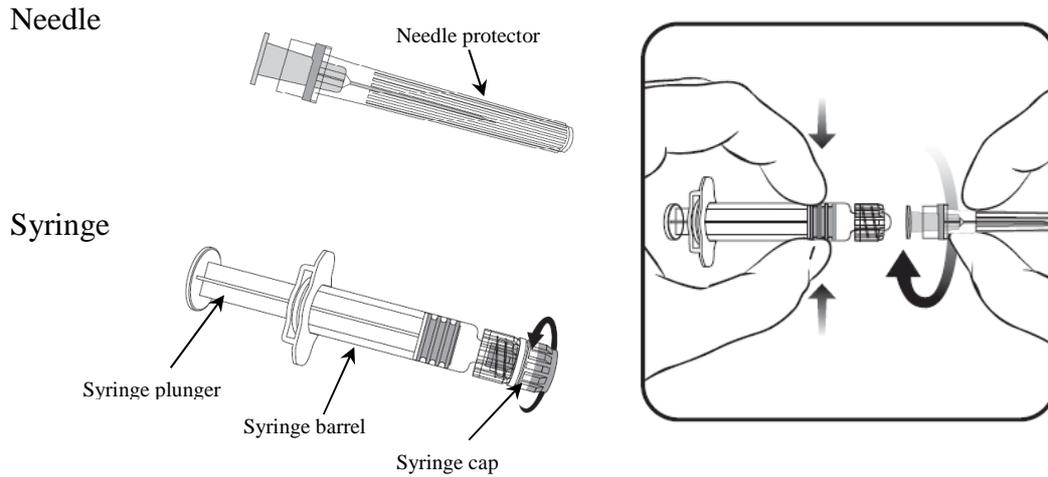
A new needle should be used to administer the vaccine.

Withdraw the entire contents of the vial.

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

Priorix-Tetra™ must be reconstituted by adding the entire content of the pre-filled syringe of solvent to the vial containing the powder.

To attach the 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.



1. Holding the syringe barrel in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.
2. To attach the 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 solvent to the powder. After the addition of the solvent to the powder, the mixture should be well shaken until the powder is completely dissolved in the solvent.

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.

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

7. Marketing Authorization Holder

GlaxoSmithKline (Thailand) Ltd.

8. Marketing Authorization Number

2C 3/54 (NB)

9. Date of authorization

10 Jun 2011 (conditional license)

27 Feb 2014 (unconditional license)

Not all presentations are available in every country.

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