1. NAME OF THE MEDICINAL PRODUCT

Priorix-Tetra

Measles, mumps, rubella and varicella vaccine

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 of subjects from the age of 9 months against measles, mumps, rubella and varicella (see also "Warnings and Precautions").

The use of Priorix-Tetra should be based on official recommendations.

4.2 Posology and method of administration

Posology

Subjects from the age of 9 months should receive 2 doses of Priorix-Tetra to ensure optimal protection against measles, mumps, rubella and varicella (see "Pharmacodynamics"). 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 subjects 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 "Instructions for Use/Handling".

4.3 Contraindications

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

Priorix-Tetra is contraindicated in subjects with severe humoral or cellular (primary or acquired) immunodeficiency (see also "Warnings and Precautions").

4.4 Special warnings and 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 "Adverse Reactions" and "Pharmacodynamics"). 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 "Posology"). 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 varicella vaccine virus has been shown to occur at a very low rate in seronegative contacts of vaccinees with rash. Transmission of the Oka varicella vaccine virus 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 "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 medicinal products and other forms of interaction

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 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 Pregnancy and Lactation

Fertility

No data available.

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.

Lactation

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

4.7 Effects on ability to drive and use machines

No studies on the effects of Priorix-Tetra on the ability to drive and use machines have been performed.

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 (≥1/10) / Common (≥1/100 to <1/10) / Uncommon (≥1/1,000 to <1/100) / Rare (≥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 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 ≥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

*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.

No clinical studies with Priorix-Tetra have been conducted in subjects > 6 years of age. The safety profile of Priorix-Tetra in subjects > 6 years of age is extrapolated from the available data with GlaxoSmithKline's MMR vaccine (Priorix) and monovalent Oka varicella vaccine (Varilrix). The frequencies of adverse reactions such as fever, rash, injection site pain, injection site swelling and injection site redness in subjects > 6 years of age who received Priorix or Varilrix were comparable to those observed in children < 6 years of age who received Priorix-Tetra.

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

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 varicella-containing vaccines in preventing confirmed varicella disease (by Polymerase Chain Reaction (PCR) or exposure to varicella case) has been evaluated in a large active controlled multicountry clinical trial in which children aged 12-22 months received two doses of Priorix-Tetra or one dose of monovalent Oka varicella vaccine (Varilrix). Vaccine efficacy against confirmed varicella of any severity and against moderate or severe confirmed varicella was demonstrated after a primary follow-up period of 2 years (median duration 3.2 years). Persistent efficacy was observed in the same study during the long term follow-up periods of 6 years (median duration 6.4 years) and 10 years (median duration 9.8 years). The data 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)
	Year 10[(1)]	95.4%	99.1%

		(95% CI: 94.0;96.4)	(95% CI: 97.9;99.6)
Monovalent Oka varicella 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)
	Year 10(1)	67.2% (95% CI: 62.3;71.5)	89.5% (95% CI: 86.1;92.1)

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 subcutaneous doses 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 (50 mIU/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 was 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.

No clinical studies to evaluate the immunogenicity of Priorix-Tetra in subjects > 6 years of age have been conducted. The immunogenicity of Priorix-Tetra in subjects > 6 years is extrapolated from available data with Priorix and Varilrix.

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, 6 and 10 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%
Year 10	98.5%	90.0%	97.7%

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 immunized 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).

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 – 8°C has been demonstrated for 8 hours after reconstitution.

6.4 Special precautions for storage

Store at 2°C – 8°C (in a refrigerator).
Do not freeze.
Store in the original packaging in order to protect from light.
The storage conditions are detailed on the packaging.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

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 Special precautions for disposal <and other handling>

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, do not administer the vaccine.
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, do not administer 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. The mixture should be well shaken until the powder is completely dissolved in the solvent.

After reconstitution, the vaccine should be used promptly.

Withdraw the entire contents of the vial.

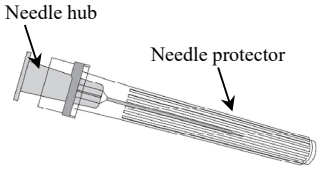
A new needle should be used to administer the vaccine.

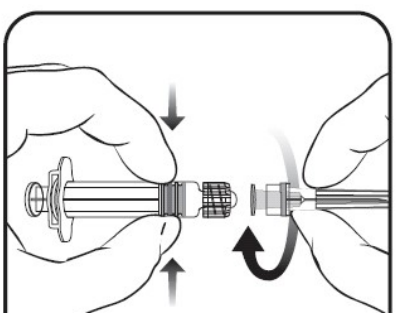
Instructions for reconstitution of the vaccine with solvent presented in pre-filled syringe

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

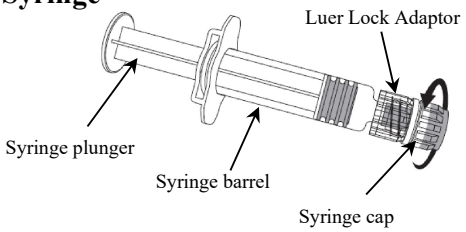
To attach the needle to the syringe, carefully read the instructions given with pictures 1 and 2. However, the syringe provided with Priorix-Tetra might be slightly different than the syringe illustrated.

Needle





Syringe



Picture 1 **Picture 2**

Always hold the syringe by the barrel, not by the syringe plunger or the Luer Lock Adaptor (LLA), and maintain the needle in the axis of the syringe (as illustrated in picture 2). Failure to do this may cause the LLA to become distorted and leak.

During assembly of the syringe, if the LLA comes off, a new vaccine dose (new syringe and vial) should be used.

1. Unscrew the syringe cap by twisting it anticlockwise (as illustrated in picture 1).

2. Attach the needle to the syringe by gently connecting the needle hub into the LLA and rotate a quarter turn clockwise until you feel it lock (as illustrated in picture 2).

3. Remove the needle protector, which may be stiff.

4. Add 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.

5. Withdraw the entire contents of the vial.

6. A new needle should be used to administer the vaccine. Unscrew the needle from the syringe and attach the injection needle by repeating step 2 above.

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

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, do not administer the vaccine.
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, do not administer the vaccine

7. <MANUFACTURER>

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GDS 016/IPI013