Priorix Tetra

1. NAME OF THE MEDICINAL PRODUCT

Priorix Tetra – powder and solvent for solution for injection.
Measles, mumps, rubella and varicella vaccine (live)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.5 ml) contains:

Measles virus[1] Schwarz strain (live, attenuated) not less than $10^{3.0}$ $CCID_{50}$[3]
Mumps virus[1] RIT 4385 strain, derived from Jeryl Lynn strain (live, attenuated) not less than $10^{4.4}$ $CCID_{50}$[3]
Rubella virus[2] Wistar RA 27/3 strain (live, attenuated) not less than $10^{3.0}$ $CCID_{50}$[3]
Varicella virus[2] OKA strain (live, attenuated) not less than $10^{3.3}$ PFU[4]

[1] produced on chick embryo cells
[2] produced on human diploid (MRC-5) cells
[3] Cell culture infective dose 50%
[4] Plaque forming units

This vaccine contains a trace amount of neomycin. See section 4.3.

Excipient with known effect
The vaccine contains 14 mg of sorbitol per dose
The vaccine contains 6.5 nanograms of para-aminobenzoic acid per dose and 583 micrograms of phenylalanine per dose (see section 4.4).
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For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
Before reconstitution, the powder is a white to slightly pink coloured cake and the solvent is a clear colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Priorix Tetra is indicated for active immunisation against measles, mumps, rubella and varicella in children from the age of 12 months up and including 12 years of age.

Use in infants aged 9-11 months could be considered under special circumstances. See section 4.2.

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

4.2 Posology and method of administration

Posology

Children from 12 months up to 12 years
Infants and children aged from 12 months up to 12 years should receive two doses (each of 0.5 ml) of Priorix-Tetra. The age at which infants or children may receive Priorix Tetra should reflect applicable official recommendations*, which vary according to the epidemiology of these diseases.

The dose interval should preferably* be between 6 weeks and 3 months. When the first dose is administered at 11 months of age, the second dose should be administered within 3 months. Under no circumstances should the dose interval be less than 4 weeks. See section 5.1.

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 two or one doses of measles, mumps and rubella and of varicella-containing vaccines.*

Children from 9 to 11 months
In case an epidemiological situation requires vaccinating infants less than 12 months of age, the first dose of Priorix Tetra can be given as from 9 months of age. A second dose of Priorix Tetra should be given three months after the first dose (see section 5.1).

Method of administration

The vaccine is to be injected by the subcutaneous route in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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.

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 or neomycin. A history of contact dermatitis to neomycin is not a contra-indication. For egg allergy, see section 4.4.

Hypersensitivity after previous administration of measles, mumps, rubella and/or varicella vaccines.

Severe humoral or cellular (primary or acquired) immunodeficiency, e.g. severe combined immunodeficiency, agammaglobulinemia and AIDS or symptomatic HIV infection or an age-specific CD4+ T-lymphocyte percentage in children below 12 months: CD4+ <25%; children between 12-35 months: CD4+ < 20%; children between 36-59 months: CD4+ < 15% (see section 4.4).

Pregnancy. Furthermore, pregnancy should be avoided for 1 month following vaccination (see section 4.6).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded. It is recommended to record the batch number as well.

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.

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.

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.

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

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

Febrile convulsions
There was an increased risk of fever and febrile convulsions 5 to 12 days after the first dose of Priorix Tetra observed as compared to concomitant administration of MMR and varicella vaccines (see sections 4.8 and 5.1).

Vaccination of subjects with a personal or family history of convulsions (including febrile convulsions) should be considered with caution. For these subjects, alternative immunisation with separate MMR and varicella vaccines should be considered for the first dose (see section 4.2). In any case vaccinees should be monitored for fever during the risk period.

Fever rates are usually high after the first dose of measles-containing vaccines. There was no indication of an increased risk of fever after the second dose.

Immunocompromised patients
Vaccination may be considered in patients with selected immune deficiencies where the benefits outweigh the risks (e.g. asymptomatic HIV subjects, IgG subclass deficiencies, congenital neutropenia, chronic granulomatous disease, and complement deficiency diseases).

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

Transmission
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 11^{th} 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.
Vaccine recipients, even those who do not develop a varicella-like rash, should attempt to avoid , whenever possible, close association with high-risk individuals susceptible to varicella for up to 6 weeks following vaccination. In circumstances where contact with high-risk individuals susceptible to

varicella is unavoidable, the potential risk of transmission of the varicella vaccine virus should be weighted against the risk of acquiring and transmitting wild-type varicella virus.
High-risk individuals susceptible to varicella include:

- Immunocompromised individuals (see sections 4.3 and 4.4)
- Pregnant women without documented positive history of varicella (chickenpox) or laboratory evidence of prior infection.
- Newborns of mothers without documented positive history of chickenpox or laboratory evidence of prior infection.

Priorix Tetra should under no circumstances be administered intravascularly or intradermally.

Thrombocytopenia
Cases of worsening of thrombocytopenia and cases of 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. These patients should be vaccinated with caution.

Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

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.

Very few reports exist on disseminated varicella with internal organ involvement following vaccination with Oka varicella vaccine strain mainly in immunocompromised subjects.
Interference with serological testing (see section 4.5).

Excipients with known effects

Priorix-Tetra contains para-aminobenzoic acid. It may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.
The vaccine contains 583 micrograms of phenylalanine per dose. Phenylalanine may be harmful for individuals with phenylketonuria (PKU).

The vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.
The vaccine contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially ‘potassium-free’.

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 [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), 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.

Due to an increased risk of fever, tenderness at the injection site, change in eating habits and irritability when Bexsero was co-administered with Priorix-Tetra, separate vaccinations can be considered when possible.

There are currently insufficient data to support the use of Priorix Tetra with any other vaccines.

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.

Serological testing
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.

Vaccine recipients should avoid use of salicylates for 6 weeks after each vaccination with Priorix Tetra (see section 4.4).

4.6 Fertility, pregnancy and lactation

Fertility
Priorix Tetra has not been evaluated in fertility studies.

Pregnancy
Pregnant women should not be vaccinated with Priorix-Tetra.

However, fetal damage has not been documented when measles, mumps, rubella or varicella vaccines have been given to pregnant women.

Pregnancy should be avoided for 1 month following vaccination. Women who intend to become pregnant should be advised to delay.

Breast-feeding
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. Priorix-Tetra is expected to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety profile presented below is based on data from clinical trials in which more than 6,700 doses of Priorix Tetra were administered subcutaneously to more than 4,000 children from 9 to 27 months of age. Events were recorded for up to 42 days after vaccination.

The most common adverse reactions following Priorix Tetra administration were pain and redness at the injection site as well as fever ≥38°C (rectal) or ≥37.5°C (axillary/oral).

Tabulated list of adverse reactions

Adverse reactions reported are listed according to the following frequency:
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)

Clinical trial data

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

* The risk of febrile convulsions following the first dose vaccination of children aged 9 to 30 months with Priorix Tetra compared with 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.
Depending on the case definition used to identify febrile convulsions in the main risk period 5 to 12 days following the first dose, incidences of febrile convulsions were 2.18 (95% CI: 1.38; 3.45) or 6.19 (95% CI: 4.71; 8.13) per 10,000 subjects for the MMRV group and 0.49 (95% CI: 0.19; 1.25) or 2.55 (95% CI: 1.67; 3.89) per 10,000 subjects for the matched control cohorts.
These data suggest one additional case of febrile convulsion per 5,882 or 2,747 subjects vaccinated with Priorix Tetra compared to matched control cohorts who received MMR or simultaneous, but separate MMR and varicella vaccination (attributable risk of 1.70 (95% CI:-1.86; 3.46) and 3.64 (95% CI: -6.11; 8.30) per 10,000 subjects, respectively) – see section 5.1.

**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 (MMRV) 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 spectrum 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 was comparable to that observed in children < 6 years of age who received Priorix-Tetra. In these clinical studies evidence has been obtained to conclude that the second dose of the MMR vaccine is better tolerated in terms of fever than the first dose, whereas reactogenicity of the varicella vaccine tends to remain similar irrespective of the dose applied. Injection site swelling is "commonly" reported in children who received Priorix-Tetra, while it is "very commonly" reported in Varilrix studies in adolescents and adults.

Post-marketing surveillance data

The following additional adverse reactions have been identified in rare occasions during post-marketing surveillance. Because they are reported voluntarily from a population of unknown size, a true estimate of frequency cannot be provided.

System Organ Class	Adverse reactions
Infections and infestations	meningitis, herpes zoster*, measles-like syndrome, mumps-like syndrome (including orchitis, epididymitis and parotitis)
Blood and lymphatic system disorders	thrombocytopenia, thrombocytopenic purpura
Immune system disorders	allergic reactions (including anaphylactic and anaphylactoid reactions)
Nervous system disorders	encephalitis, cerebellitis, cerebrovascular accident, Guillain Barré syndrome, transverse myelitis, peripheral neuritis, cerebellitis like symptoms (including transient gait disturbance and transient ataxia)
Vascular disorders	vasculitis
Skin and subcutaneous tissue disorders	erythema multiforme, varicella-like rash
Musculoskeletal and connective tissue disorders	arthralgia, arthritis

* This adverse drug reaction reported after vaccination is also a consequence of wild-type varicella infection. There is no indication of an increased risk of herpes zoster occurrence following vaccination compared with wild-type disease.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (https://sideeffects.health.gov.il/).Additionally, you should also report to GSK Israel (il.safety@gsk.com)

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Vaccines,Viral vaccine, ATC code J07BD54

Efficacy

The efficacy of GlaxoSmithKline (GSK)'s monovalent Oka varicella (Varilrix) and Priorix Tetra vaccines in preventing varicella disease has been evaluated in a large randomised multicountry clinical trial, which included GSK combined measles-mumps-rubella vaccine (Priorix) as active control. The trial has been conducted in Europe where no routine varicella vaccination was implemented at that time. Children aged 12-22 months received two doses of Priorix Tetra six weeks apart or one dose of Varilrix. Vaccine efficacy against epidemiologically confirmed or PCR (Polymerase Chain Reaction) confirmed varicella of any severity (defined using a prespecified scale) Priorix Tetra 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% (95% CI: 94.0;96.4)	99.1% (95% CI: 97.9;99.6)
Varilrix (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

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.
The effectiveness of two doses of Priorix Tetra during varicella outbreaks in day care centres in Germany, where routine varicella vaccination is recommended for children as of 11 months of age, was 91% (95% CI: 65;98) against any disease and 94% (95% CI: 54;99) against moderate disease.

The effectiveness of one dose of Varilrix was estimated in different settings (outbreaks, case-control and database studies) and ranged from 20%-92% against any varicella disease and from 86%-100% against moderate or severe disease.

Immune response

Several clinical studies evaluated the immune response elicited by Priorix-Tetra administered subcutaneously. Anti-measles, anti-mumps and anti-rubella antibody titres were determined using commercially available enzyme-linked immunosorbent assays (ELISA). In addition, anti-mumps antibodies were titrated using a plaque-reduction neutralisation assay. These serological parameters are widely accepted as surrogate markers for immune protection. A modified commercial indirect immunofluorescence assay (IFA, meanwhile discontinued) and a commercial ELISA were used to compare the immune response against varicella elicited by Priorix Tetra to that observed with GSK varicella vaccine.

In three clinical trials conducted in Europe (Austria, Finland, Germany, Greece, Poland) approximately 2,000 previously unvaccinated children from 11 to 23 months of age received 2 doses of Priorix Tetra with an interval between doses of 6 weeks. Seroconversion rates and geometric mean antibody concentrations/titres (GMC/GMT) are summarized in the table below.

Antibody Test (cut-off)	**Post dose 1**		**Post dose 2**	
	Seroconversion rates (95 % CI)	GMC/GMT (95 % CI)	Seroconversion rates (95 % CI)	GMC/GMT (95 % CI)
Measles ELISA (150mIU/ml)	96.4% (CI: 95.5;97.2)	3184.5 (CI: 3046.5;3328.7)	99.1% (CI: 98.6;99.5)	4828.6 (CI: 4644.3;5020.1)
Mumps ELISA (231U/ml)	91.3% (CI: 90.0;92.5)	976.7 (CI: 934.8;1020.5)	98.8% (CI: 98.2;99.2)	1564.4 (CI: 1514.6;1615.8)
Neutralisation (1:28)	95.4% (CI: 94.3;96.3)	147.0 (CI: 138.6;155.8)	99.4% (CI: 98.9;99.7)	478.4 (CI: 455.1;503.0)
Rubella ELISA (4IU/ml)	99.7% (CI: 99.4;99.9)	62.2 (CI: 60.0;64.5)	99.9% (CI: 99.6;100)	119.7 (CI: 116.4;123.1)
Varicella IFA (1:4)	97.2% (CI: 96.3;97.9)	97.5 (CI: 92.2;103.1)	99.8% (CI: 99.5;100)	2587.8 (CI: 2454.0;2728.9)
ELISA (50mIU/ml)	89.4% (CI: 87.8;90.8)	112.0 (CI: 93.5;134.0)	99.2% (CI: 98.5;99.6)	2403.9 (CI: 1962.4;2944.6)

Seroconversion rates and geometric mean antibody concentrations/titres were similar to those observed after separate vaccination with Varilrix and Priorix.

In infants vaccinated at 11 months of age, the proportion of infants with protective measles titers (i.e., $\geq$ 150 mIU/mL) after the first dose is 91-92%, lower than the proportion observed when the first dose is administered since the age of 12 months.

The second dose of Priorix Tetra induced an increase in seroconversion rates and/or antibody levels for the measles, mumps and rubella vaccine components. Therefore, to avoid infection during the interval between doses it is preferred that the second dose be administered within three months following the first dose.

Data suggest a higher efficacy and a decrease in breakthrough varicella following two doses of vaccine with respect to one dose. This correlates with an increase in anti-varicella antibodies elicited by the second dose, which suggests that the second dose of varicella antigen acts as a booster.

The immune response of Priorix Tetra administered as a second dose of MMR vaccine in children 24months to 6 years of age was evaluated in 2 clinical studies. Children were previously primed with respectively an MMR vaccine or with an MMR vaccine co-administered with a live attenuated varicella vaccine. Seropositivity rates for anti-varicella antibodies were 98.1% (IFA) in children 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 100% for anti-measles, mumps, rubella antibodies in both studies.

Immune response in subjects > 6 years of age

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.

Immune response in children aged 9 to 10 months
A clinical trial conducted in Asia (Singapore) enrolled 300 healthy children 9 to 10 months of age at the time of first vaccine dose. Of these, 153 subjects received 2 doses of Priorix Tetra with an interval between doses of 3 months and 147 subjects received Priorix and Varilrix. Seroconversion rates and geometric mean antibody concentrations/titres were similar to those observed after separate vaccination with Varilrix and Priorix. 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. The seroconversion rate reported for measles in infants 9 to 10 months of age following 1 dose of Priorix Tetra was 93.3% (95% CI: 87.6;96.9). Infants in their first year of life may not respond sufficiently to the components of the vaccine due to the possible interference with maternal antibodies. Therefore a second dose of Priorix Tetra should be given three months after the first dose.

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

As robust efficacy data against varicella disease up to 10 years are provided above (see subsection "Efficacy") and since there is no threshold for protection against varicella disease established with the obtained immunological data, anti-varicella antibody persistence data are not provided.

Post-Marketing Observational Safety Surveillance Study

The risk of febrile convulsions following the first dose of Priorix Tetra was assessed in a retrospective database analysis in children aged 9 to 30 months (see section 4.8).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

A repeated dose toxicity study in animals did not reveal any local or systemic toxicity of the vaccine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Lactose anhydrous
Amino acids (containing phenylalanine) for injections
Mannitol
Sorbitol
Medium 199 (containing phenylalanine, para-aminobenzoic acid, sodium and potassium)

Solvent:
Water for injection

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 product/vaccine is indicated on packaging materials.

After reconstitution, the vaccine should be administered promptly or kept in the refrigerator (2°C – 8°C). If it is not used within 24 hours, it should be discarded..

6.4 Special precautions for storage

Store and transport refrigerated (2°C – 8°C).

Do not freeze.

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

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder in a vial (type I glass) with a stopper (butyl rubber).
0.5 ml of solvent in an ampoule (type I glass).
Pack sizes of 1, 10, 20 or 50.

Powder in a vial (type I glass) with a stopper (butyl rubber).
0.5 ml of solvent in a pre-filled syringe (type I glass) with plunger stopper (butyl rubber) with or without separate needles in the following pack sizes:1, 10, 20 or 50.

Not all pack sizes may be marketed.

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

Solvent in ampoule:

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

The vaccine 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.

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.

Withdraw the entire contents of the vial.

A new needle should be used to administer the vaccine.

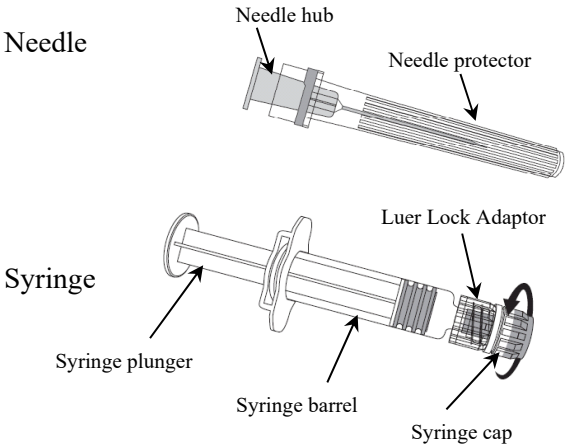
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

<u>Solvent in a pre-filled syringe:</u>

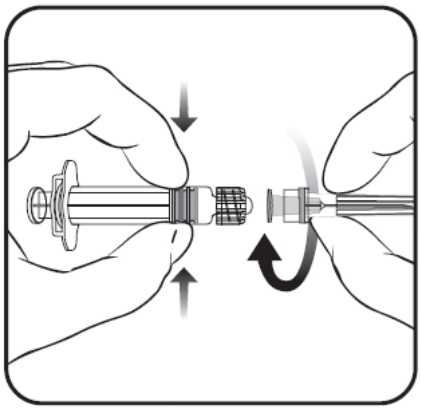
The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance before administration. In the event of either being observed, do not administer the vaccine.

The vaccine is 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 (without screw thread) than the syringe illustrated.
In that case, the needle should be attached without screwing.



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).

Whether the LLA is rotating or not, please follow the below steps:

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.

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.

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

7. MANUFACTURER

GlaxoSmithKline Biologicals S.A., Rixensart, Belgium.

8. LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

9. LICENSE NUMBER

138-98-31847

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PriTet DR V10