DATA SHEET

Name of Medicinal Product

PRIORIX-TETRA®

Live attenuated measles, mumps, rubella and varicella vaccine

Presentation

PRIORIX-TETRA is a sterile lyophilised mixed preparation of the attenuated Schwarz measles, RIT 4385 mumps (derived from Jeryl Lynn strain), Wistar RA 27/3 rubella and OKA varicella strains of viruses, separately produced in chick embryo cells (mumps and measles) or human diploid MRC_5 cells (rubella and varicella).

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).

Each 0.5 mL dose of the reconstituted vaccine contains not less than $10^{3.0}$ $CCID_{50}$ 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 $10^{3.3}$ PFU of the varicella virus strains.

Clinical Particulars

Therapeutic indications

PRIORIX-TETRA is indicated for active immunisation in infants and children from the age of 9 months up to 12 years of age inclusive against measles, mumps, rubella and varicella.

Posology and method of administration

Posology

Infants and children 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 Pharmacodynamic Effects).

An interval of at least 6 weeks between doses is recommended. As with other live 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 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

Method of administration
The vaccine is to be injected subcutaneously (SC) or intramuscularly (IM).
The preferred injection site is the deltoid region of the upper arm.

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

For information on instructions for preparation or reconstitution see *Instructions for use, handling and disposal.*

Contraindications

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

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

It is contra-indicated to administer PRIORIX-TETRA to pregnant females. Furthermore, pregnancy should be avoided for three months after vaccination (*see Pregnancy*).

PRIORIX-TETRA should not be given to children with impaired immune function. These include patients with primary or secondary immunodeficiencies.

Special warnings and special precautions for use
As with other vaccines, the administration of PRIORIX-TETRA should be postponed in children 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.

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 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.

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 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 children with a history of febrile convulsions or a family history of convulsions should be considered with caution Alternative immunisation of these children 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.

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. 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.

PRIORIX-TETRA should under no circumstances be administered intravascularly or intradermally. Accidental intravascular administration may give rise to severe reactions or even shock. Immediate measures depend on the severity of the reaction.

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

Cases of worsening of thrombocytopenia and recurrence of thrombocytopenia in children who suffered thrombocytopenia after the first dose have been reported following vaccination with live measles, mumps and rubella vaccines. In such cases, the risk-benefit of immunising with PRIORIX-TETRA should be carefully evaluated.

The use of PRIORIX-TETRA in asymptomatic HIV positive individuals 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.

Interaction with other medicaments 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 children 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.

Pregnancy and lactation

Pregnancy

It is contraindicated to administer PRIORIX-TETRA to pregnant women. Furthermore, pregnancy should be avoided for three months after vaccination. 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**.**

Effects on ability to drive and use machines

Not applicable.

Undesirable effects

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.

Frequencies per dose are defined as follows:
Very common: ≥ 1/10
Common: ≥ 1/100 and < 1/10
Uncommon: ≥ 1/1000 and < 1/100
Rare: ≥ 1/10000 and < 1/1000
Very rare: < 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: crying, nervousness, insomnia

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

* 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 concomittant administration of measles-mumps-rubella and varicella vaccines at separate injection sites.

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

Infections and infestations: Meningitis, orchitis, epididymitis, mumps-like syndrome

Blood and lymphatic system disorders: Thrombocytopenia, thrombocytopenic purpura

Immune system disorders: Allergic reactions (including anaphylactic and anaphylactoid reactions)

Nervous system disorders: encephalitis, cerebrovascular accident, cerebellitis, cerebellitis like symptoms,, Guillain Barré syndrome, transverse myelitis, peripheral neuritis

Skin and subcutaneous tissue disorders: Erythema multiforme

Musculoskeletal and connective tissue disorders: Arthralgia, arthritis

General disorders and administration site conditions: Kawasaki syndrome

Overdose
Insufficient data are available

Pharmacological Properties

Pharmacodynamic properties
Pharmaco-therapeutic group: Viral attenuated vaccine, ATC code J07BD54

Efficacy and effectiveness
In clinical trials, it has been shown that the vast majority of subjects who received varicella vaccines and are exposed to wild-type virus were either completely protected from chickenpox or developed a milder form of the disease (breakthrough varicella).

The efficacy of GlaxoSmithKline (GSK)'s OKA/RIT varicella vaccines in preventing confirmed varicella disease (clinical breakthrough varicella was 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) or one dose of VARILRIX (N = 2263). 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 1.

Table 1: 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

Immune response
Seroconversion rates elicited by two 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 2 below:

Table 2: Seroconversion rates elicted by 2 doses of PRIORIX-TETRA

Antibody Test (cut-off)	Post dose 1	Post dose 2
Measles		

ELISA (150mIU/ml)	96.4%	99.1%
Mumps **ELISA (231U/ml)** **Neutralisations (1:28)**	 91.3% 95.4%	 98.8% 99.4%
Rubella **ELISA (4IU/ml)**	 99.7%	 99.9%
Varicella **IFA (1:4)** **ELISA 50mIU/mL**	 97.2% 89.4%	 99.8% 99.2%

ELISA: Enzyme Linked Immuno Sorbent Assay
IFA: Immunofluorescence Assay

In a large efficacy trial two years after vaccination with two doses of PRIORIX-TETRA; seropositivity rates for anti-varicella antibodies were 99.4% (ELISA) and 99.2% (IFA) and respectively 99.1%, 90.5% and 100% for anti-measles, mumps and rubella antibodies (ELISA).
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.

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The immune response of PRIORIX-TETRA administered as a second dose of MMR vaccine in children 24 months 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 and rubella antibodies in both studies.

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.

Post-Marketing Observational Safety Surveillance Study

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

The study included 82,656 children immunized with 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).

Pharmacokinetic properties
Evaluation of pharmacokinetic properties is not required for vaccines.

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

Pharmaceutical Particulars

List of excipients
Lactose, amino acids, mannitol, sorbitol, neomycin sulphate (residual), and water for injections.

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

Shelf life
2 years.

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

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.

Nature and contents of container
PRIORIX-TETRA is presented as a cake with a slightly pink colour in a glass vial. The sterile diluent is clear peach to fuschia and presented in a glass prefilled syringe or ampoule. Due to minor variation of its pH, the reconstituted vaccine may vary in colour from colourless to light pink without deterioration of the vaccine potency. This is normal and does not impair the performance of the vaccine. In the event of other variation being observed, discard the vaccine.

Vials/prefilled syringes are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.

Instructions for use, handling and disposal
The diluent should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the diluent.

The vaccine is reconstituted by adding the entire contents of the supplied container of diluent to the vial containing the powder. After the addition of the diluent to the powder, the mixture should be well shaken until the powder is completely dissolved.

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.

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

Medicine Classification
Prescription Medicine

Package Quantities
PRIORIX-TETRA vaccine: monodose glass vials and pre-filled syringe diluent in packs of 1 and 10 with two separate needles. Packs of 1 and 10 without needles.

PRIORIX-TETRA vaccine: monodose glass vials and diluent ampoules in packs of 1 and 10.

PRIORIX-TETRA vaccine: monodose glass vials in packs of 10.

Not all pack sizes may be marketed

Name and Address
GlaxoSmithKline NZ Limited
AMP Centre
Cnr Albert & Customs Street
Private Bag 106600
Downtown
Auckland
NEW ZEALAND

ph (09) 367 2900
fax (09) 367 2910

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