For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

PRIORIX®

Measles, Mumps and Rubella Vaccine (Live) IP

1. NAME OF THE MEDICINAL PRODUCT

Measles, Mumps and Rubella Vaccine (Live) IP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PRIORIX is a lyophilised mixed preparation of the attenuated Schwarz measles, RIT 4385 mumps (derived from Jeryl Lynn strain) and Wistar RA 27/3 rubella strains of viruses, separately obtained by propagation either in chick embryo tissue cultures (mumps and measles) or MRC-5 human diploid cells (rubella).

Each dose (0.5 ml) of the reconstituted vaccine contains:

Live attenuated measles virus (Schwarz strain) [propagated in chick embryo tissue cultures]: $\geq 10^{3.0}$ $CCID_{50}$
Live attenuated mumps virus (RIT 4385 strain) [propagated in chick embryo tissue cultures]: $\geq 10^{3.7}$ $CCID_{50}$
Live attenuated rubella virus (RA27/3 strain) [propagated in MRC5 human diploid cells]: $\geq 10^{3.0}$ $CCID_{50}$

Water for injections IP qs 0.5 ml

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

For a full list of excipients, see section *6.1 List of Excipients*

PRIORIX meets the World Health Organisation requirements for manufacture of biological substances and for measles, mumps and rubella vaccines and combined vaccines (live).

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The lyophilized Measles-Mumps-Rubella component is a white to slightly pink powder.

The solvent is a clear and colorless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PRIORIX is indicated for the active immunisation against measles, mumps and rubella.

4.2 Posology and method of administration

Posology

The use of *PRIORIX* should be based on official recommendations.

The dose is 0.5 ml. A second dose should be given according to official recommendations.

PRIORIX may be used in individuals who have previously been vaccinated with another monovalent or combined measles, mumps and rubella vaccine.

Method of administration

PRIORIX is for subcutaneous injection; intramuscular injection is also possible (see section *4.4 Special warnings and precautions for use* and *5.1 Pharmacodynamic properties*).

The vaccine should preferably be administered subcutaneously in patients with thrombocytopenia or a coagulation disorder (see section *4.4 Special warnings and precautions for use*).

For instructions on reconstitution of the medicinal product before administration, see section *6.6 Special precautions for disposal and other handling*.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section *6.1 List of excipients* or neomycin. A history of contact dermatitis to neomycin is not a contraindication. For hypersensitivity reactions to egg proteins, see section *4.4 Special warnings and precautions for use*.

Severe humoral or cellular (primary or acquired) immunodeficiency, e.g. severe combined immunodeficiency, agammaglobulinaemia 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 Special warnings and precautions for use*.

Pregnancy. In addition, pregnancy should be avoided within two months following vaccination (see section *4.6 Pregnancy and lactation*).

As with other vaccines, administration of *PRIORIX* must be postponed in subjects suffering from severe febrile illnesses. A minor infection, such as a cold, should not result in the deferral of vaccination.

4.4 Special warnings and precautions for use

As with all injectable vaccines, it is recommended that surveillance and appropriate medical treatment should always be available in the rare event of an anaphylactic reaction following administration of the vaccine.

Alcohol and other disinfecting agents applied to the skin must be allowed to evaporate before any injection of the vaccine as they can inactivate the attenuated viruses in the vaccine.

Infants below 12 months of age may not respond sufficiently to the measles component of the vaccine, due to the possible persistence of maternal measles antibodies. This should not preclude the use of the vaccine in younger infants (<12 months) since vaccination may be indicated in some situations such as high-risk areas. In these circumstances revaccination at or after 12 months of age should be considered (see section *5.1 Pharmacodynamic properties*).

PRIORIX must be administered with caution to individuals with Central Nervous System (CNS) disorder, susceptibility to febrile convulsions or family history of convulsions. Vaccinees with a history of febrile convulsions must be closely monitored.

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 increased risk of developing an immediate-type hypersensitivity reaction after vaccination, although these types of reactions are observed only very rarely. Individuals who have experienced an anaphylactic reaction after egg ingestion must be vaccinated with extreme caution, with appropriate treatment on hand should an anaphylactic reaction occur.

Patients with rare hereditary problems of fructose intolerance should not be vaccinated with *PRIORIX*, as it contains sorbitol.

Limited protection against measles may be obtained by vaccination up to 72 hours after natural exposure to the measles virus.

Syncope (fainting) can occur following any vaccination, or even before, especially in adolescents as a psychogenic response to the injection needle. 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 any injury from fainting.

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

PRIORIX SHOULD UNDER NO CIRCUMSTANCES BE ADMINISTERED INTRAVASCULARLY.

Thrombocytopenia

Cases of worsening of thrombocytopenia and recurrence of thrombocytopenia have been reported in subjects who have suffered thrombocytopenia after the first dose following

vaccination with live measles, mumps and rubella vaccines. Thrombocytopenia associated with the measles, mumps and rubella vaccination is rare and generally resolves spontaneously. In patients with thrombocytopenia or a history of thrombocytopenia after measles, mumps or rubella vaccination the benefit-risk ratio of administering *PRIORIX* must be carefully evaluated. These patients must be vaccinated with caution and preferably via the subcutaneous route.

Immunocompromised patients

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

Immunoscompromised patients who have no contraindication for this vaccination (see section *4.3 Contraindications*) may not respond as well as immunocompetent subjects; some of these patients may therefore become infected with measles, mumps or rubella viruses in case of contact, despite appropriate vaccination. These patients must be monitored carefully for signs of measles, parotitis and rubella.

Transmission

Transmission of the measles and mumps viruses from vaccinees to non-immunized contacts has never been documented. Pharyngeal excretion of the rubella and measles virus is known to occur generally between 7 and 28 days after vaccination, with peak excretion around the 11^{th} day. However, there is no evidence of transmission of these excreted vaccine viruses to non-immunised contacts. Transmission of the rubella vaccine virus to infants via breast milk or via the transplacental route has been documented with no apparent clinical signs.

4.5 Interaction with other medicinal products and other forms of interaction

PRIORIX can be administered simultaneously (but at different injection sites) 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 serotype C conjugated vaccine (MenC), varicella zoster vaccine (VZV), oral polio vaccine (OPV) and 10-valent pneumococcal conjugate vaccine, in accordance with official recommendations.

If not given simultaneously, an interval of at least one month is recommended between administration of *PRIORIX* and other live attenuated vaccines.

There are no data on the administration of *PRIORIX* with any other vaccine.

If a tuberculin test is to be performed it should be carried out before or at the same time as vaccination, since it has been reported that 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, the tuberculin test must not be performed during this post-vaccination period in order to avoid false negative results.

In subjects who have received human gamma globulins or a blood transfusion, vaccination should be delayed for 3 months or longer (up to 11 months) depending on the dose of human immunoglobulins administered, because of the risk of vaccine failure due to passively acquired measles, mumps and rubella antibodies.

4.6 Pregnancy and lactation

Fertility

PRIORIX has not been evaluated in fertility studies.

Pregnancy

Pregnant women must not be vaccinated with *PRIORIX*.

However, no harmful effect on the foetus has been documented after administration of measles, mumps and rubella vaccines in pregnant women.

Even if a theoretical risk cannot be excluded, no case of congenital rubella syndrome has been reported in more than 3500 susceptible women who were unknowingly in the early stages of pregnancy when administered a rubella vaccine. Therefore, inadvertent vaccination of unknowingly pregnant women with measles, mumps and rubella vaccines should not be a reason for termination of pregnancy.

Pregnancy should be avoided within two months following vaccination. Women who intend to become pregnant should be advised to delay.

Breast-feeding

There are limited data on *PRIORIX* during breast-feeding. Studies have shown that breast-feeding postpartum women vaccinated with live attenuated rubella vaccines may excrete the virus in breast milk and transmit it to breast-fed infants with no apparent clinical symptoms. The benefit/risk ratio of vaccinating the mother must be evaluated only in cases where the child is confirmed or suspected to be immunodeficient (see section *4.3 Contraindications*).

4.7 Effects on ability to drive and use machines

PRIORIX has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety profile described below is based on a total of approximately 12,000 subjects vaccinated with *PRIORIX* during clinical trials.

Adverse reactions which may occur following the use of a combined measles, mumps and rubella combined vaccine correspond to those observed after administration of the monovalent vaccines alone or in combination.

In controlled clinical trials, signs and symptoms were actively monitored during a 42-day follow-up period. The vaccinees were also requested to report any clinical events during the study period.

The most common adverse reactions following *PRIORIX* administration were injection–site redness and fever ≥38°C (rectal) or ≥37.5°C (axillary/oral).

List of adverse reactions

The adverse reactions reported are listed according to the following frequencies:

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)

Clinical trial data

Infections and infestations
Common: upper respiratory tract infection.
Uncommon: otitis media.

Blood and lymphatic system disorders
Uncommon: lymphadenopathy.

Immune system disorders
Rare: Allergic reactions.

Metabolism and nutrition disorders
Uncommon: anorexia.

Psychiatric disorders
Uncommon: nervousness, abnormal crying, insomnia.

Nervous system disorders
Rare: febrile convulsions.

Eye disorders
Uncommon: conjunctivitis.

Respiratory, thoracic and mediastinal disorders
Uncommon: bronchitis, cough.

Gastrointestinal disorders
Uncommon: parotitis, diarrhea, vomiting.

Skin and subcutaneous tissue disorders
Common: rash.

General disorders and administration site conditions
Very common: redness at the injection site, fever ≥38°C (rectal) or ≥37.5 °C (axillary/oral)

Common: pain and swelling at the injection site, fever >39.5°C (rectal) or >39°C (axillary/oral).

In general, the frequency of adverse reactions was identical for the first and second vaccine doses, with the exception of pain at the injection site, which was '"common" after the first vaccine dose, and "very common" after the second vaccine dose.

Post-marketing surveillance data

The following adverse reactions have been identified on rare occasions during post-marketing surveillance. These effects are reported on a voluntary basis and for a population of unknown size. Consequently, no exact estimate of frequency can be made.

Infections and infestations
Meningitis, measles-like syndrome, mumps-like syndrome (including orchitis, epididymitis and parotitis).

Blood and lymphatic system disorders
Thrombocytopenia, thrombocytopenic purpura.

Immune system disorders
Anaphylactic reactions.

Nervous system disorders
Encephalitis*, cerebellitis, cerebellitis-like syndrome (including transient gait disturbance and transient ataxia), Guillain-Barré syndrome, transverse myelitis, peripheral neuritis.

Vascular disorders
Vasculitis.

Skin and subcutaneous tissue disorders
Erythema multiform.

Musculoskeletal and connective tissue disorders
Arthralgia, arthritis.

*Cases of encephalitis have been reported with a frequency below 1 per 10 million doses. The risk of encephalitis following administration of the vaccine is far below the risk of encephalitis caused by natural infections (measles: 1 in 1,000 to 2,000 cases, mumps: 2-4 in 1,000 cases, rubella: approximately 1 in 6,000 cases).

Accidental intravascular administration may give rise to severe reactions or even shock. Immediate measures depend on the severity of the reaction (see section *4.4 Special warnings and precautions for use*).

4.9 Overdose

Cases of overdose (up to twice the recommended dose) have been reported during post-marketing surveillance. No adverse reactions have been associated with the overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Viral vaccine, ATC code J07BD52

Immune response in children aged 12 months and older

In clinical studies conducted in children aged 12 months to 2 years, *PRIORIX* has shown high immunogenicity.

Vaccination with a single dose of *PRIORIX* induces the antibody formation against measles in 98.1 %, against mumps in 94.4% and against rubella in 100% of initially seronegative vacinees.

Two years after the primary vaccination, seroconversion rates were 93.4 % for measles, 94.4% for mumps and 100% for rubella.

Although there are no data available concerning the protective efficacy of *PRIORIX*, immunogenicity is regarded as an indication of protective efficacy. However, some field studies have reported that protective efficacy against mumps may be lower than the seroconversion rates observed for this disease.

Immune response in infants aged 9 to 10 months

A clinical trial was conducted in 300 healthy infants aged 9 to 10 months at the time of first vaccine dose. Of these, 147 received *PRIORIX* and *VARILRIX* concomitantly. Seroconversion rates for measles, mumps and rubella were 92.6%, 91.5% and 100% respectively. The seroconversion rates reported following the second vaccination dose administered 3 months after the first dose were 100% for measles, 99.2% for mumps and 100% for rubella. Therefore a second dose of *PRIORIX* must be administered within three months following the first dose to obtain optimal immune responses.

Adolescents and adults

The safety and immunogenicity of *PRIORIX* in adolescents and adults have not been specifically studied during clinical trials.

Intramuscular route of administration

A limited number of subjects received *PRIORIX* intramuscularly during clinical trials. Seroconversion rates for the 3 vaccine components were comparable to those obtained after subcutaneous administration.

5.2 Pharmacokinetic properties

Pharmacokinetic studies are not necessary for vaccines.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional safety studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Vaccine (Lyophilized Powder): Amino acids, Lactose (anhydrous), Mannitol, & Sorbitol.
Diluent (Solvent): 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

24 months.

The vaccine must be injected immediately after reconstitution. If this is not possible, it must be stored at 2°C - 8°C and used within 8 hours of reconstitution.

The expiry date is indicated on the label & packaging.

6.4 Special precautions for storage

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

Do not freeze.

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

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

Keep out of reach of children.

6.5 Nature and contents of container

Powder in vial (type I glass) sealed with a rubber stopper.

0.5 ml solution in pre-filled syringe (type I glass) with a plunger stopper (rubber) with or without needles.

OR

0.5 ml of solvent in an ampoule (type I glass).

Pack sizes of 1, 10 or 100.

All pack presentations may not be marketed in India.

6.6 Special precautions for disposal and other handling

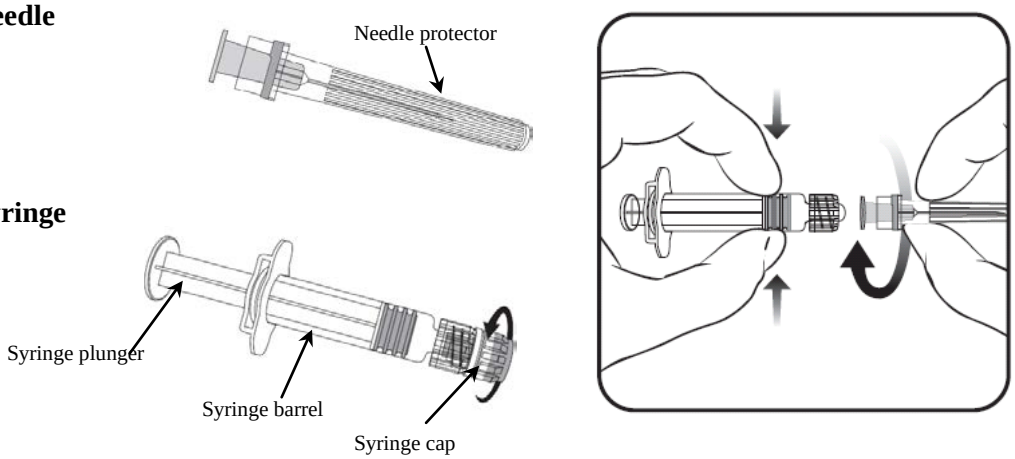
The solvent and reconstituted vaccine must be inspected visually for the presence of foreign particles and/or any change in physical appearance prior to administration. In the event of either case, discard the solvent or reconstituted vaccine.

The vaccine must be reconstituted by adding the entire contents of the pre-filled syringe / ampoule of solvent supplied to the vial containing the powder.

Instructions on use of the pre-filled syringe

To attach the needle to the syringe, please refer to the illustration below. However please note that the syringe provided with *PRIORIX* may be slightly different (without a screw thread) from the syringe shown.

In this case, the needle requires no screwing to be attached to the syringe.



1. Hold the syringe **barrel** in one hand (avoid holding the syringe by its plunger), and unscrew 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 can sometimes be slightly stiff, from the needle.

Add the solvent to the powder. After addition of the solvent to the powder, the mixture should be shaken well until the powder is completely dissolved in the solvent.

Due to minor variations in pH, the reconstituted vaccine may vary in colour from light peach to fuchsia pink without deterioration of the vaccine potency.

Withdraw the entire contents of the vial and administer.

A new needle must be used to administer the vaccine.

Contact with disinfectants must be avoided (see section *4.4 Special warnings and precautions for use*).

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Asia Private Limited
Registered Office:
Patiala Road,
Nabha (Punjab) 147201, India.

8. MARKETING AUTHORISATION NUMBER(S)

Not applicable

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 24th March 1999.

PRIORIX and *VARILRIX* are registered trademarks of GlaxoSmithKline.

PRX/PI/IN/2016/01 dated 15th April 2016.

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