PRIORIX

1. NAME OF THE MEDICINAL PRODUCT

PRIORIX
Powder and solvent for solution for injection
Measles, Mumps and Rubella vaccine (live)

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 $10^{3.7}$ $CCID_{50}$[3]
Live attenuated rubella virus[2] (Wistar RA 27/3 strain) not less than $10^{3.0}$ $CCID_{50}$[3]

[1] produced in chick embryo cells
[2] produced in human diploid (MRC-5) cells
[3] Cell Culture Infective Dose 50%

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

Excipients with known effect:
The vaccine contains 9 mg of sorbitol.
The vaccine contains 6.5 nanograms of para-aminobenzoic acid per dose and 334 micrograms of phenylalanine per dose (see section 4.4).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
The lyophilised Measles-Mumps-Rubella component is a white to slightly pink powder.
The solvent is a clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PRIORIX is indicated for active immunisation of children from the age of 9 months or older, adolescents and adults against measles, mumps and rubella.

For use in children between 9 to 12 months of age see sections 4.2, 4.4 and 5.1.

4.2 Posology and method of administration

Posology

The use of PRIORIX should be based on official recommendations.

Individuals 12 months of age or older
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.

Infants between 9 and 12 months of age
Infants in their first year of life may not respond sufficiently to the components of the vaccines. In case an epidemiological situation requires vaccinating infants in their first year of life (e.g. outbreak or travel to endemic regions), a second dose of PRIORIX should be given in the second year of life, preferably within three months after the first dose. Under no circumstances should the interval between doses be less than four weeks (see sections 4.4 and 5.1).

Infants less than 9 months of age
The safety and efficacy of PRIORIX in infants under 9 months of age has not been established.

Method of administration

PRIORIX is for subcutaneous injection, although it can also be given by intramuscular injection , preferably in the deltoid region or in the anterolateral area of the thigh.
(see sections 4.4 and 5.1).

The vaccine should preferably be administered subcutaneously in patients with thrombocytopenia or any coagulation disorder (see section 4.4).

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

4.3 Contraindications

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 contraindication. For hypersensitivity reactions to egg proteins, see section 4.4.

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).

As with other vaccines, the administration of PRIORIX should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

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.

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 (see sections 4.2 and 5.1).

Due caution should be employed in administration of PRIORIX to individuals with Central Nervous System (CNS) disorder, susceptibility to febrile convulsions or family history of convulsions. Vaccinees with a history of febrile convulsions should be closely followed-up.

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 in 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.

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

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.

PRIORIX SHOULD UNDER NO CIRCUMSTANCES BE ADMINISTERED INTRAVASCULARLY.

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. MMR-associated thrombocytopenia is rare and generally self-limited. In patients with existing thrombocytopenia or a history of thrombocytopenia after measles, mumps or rubella vaccination the risk-benefit of administering PRIORIX should be carefully evaluated. These patients should be vaccinated with caution and preferably using subcutaneous route.

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 or rubella in case of contact, despite appropriate vaccine administration. These patients should be monitored carefully for signs of measles, parotitis and rubella.

Transmission

Transmission of measles and mumps virus from vaccinees to susceptible contacts has never been documented. Pharyngeal excretion of the rubella and measles virus is known to occur about 7 to 28 days after vaccination with peak excretion around the 11th day. However, there is no evidence of transmission of these excreted vaccine viruses to susceptible contacts. Transmission of the rubella vaccine virus to infants via breast milk as well as transplacental transmission has been documented without any evidence of clinical disease.

Excipients with known effects

Priorix contains para-aminobenzoic acid. It may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.
The vaccine contains 334 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 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), reduced antigen 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), varicella zoster vaccine (VZV), oral polio vaccine (OPV) and pneumococcal conjugate vaccine in accordance with local recommendations.

Due to an increased risk of fever, tenderness at the injection site, change in eating habits and irritability when Bexsero was co-administered with a combined measles-mumps-rubella-varicella (MMR-V) vaccine, separate vaccination with PRIORIX can be considered when possible.

There are no data to support the use of PRIORIX with any other vaccines.

If PRIORIX is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

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

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 three months or longer (up to 11 months) depending on the dose of human globulins administered because of the likelihood of vaccine failure due to passively acquired measles, mumps and rubella antibodies.

4.6 Fertility, pregnancy and lactation

Fertility

PRIORIX has not been evaluated in fertility studies.

Pregnancy
Pregnant women should not be vaccinated with PRIORIX.

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

Even if a theoretical risk cannot be excluded yet, no cases of congenital rubella syndrome have been reported in more than 3,500 susceptible women who were unknowingly in early stages of pregnancy when vaccinated with rubella containing vaccines. Therefore, inadvertent vaccination of unknowingly pregnant women with measles, mumps and rubella containing vaccines should not be a reason for termination of pregnancy.

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

Breast-feeding

There is limited experience with PRIORIX during breast-feeding. Studies have shown that breast-feeding postpartum women vaccinated with live attenuated rubella vaccines may secrete the virus in breast milk and transmit it to breast-fed infants without evidence of any symptomatic disease. Only in the event the child is confirmed or suspected to be immunodeficient, risks and benefits of vaccinating the mother should be evaluated (see section 4.3).

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 presented below is based on a total of approximately 12,000 subjects administered PRIORIX in clinical trials.

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

In controlled clinical studies, 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).

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)

Clinical trial data

System Organ Class	Frequency	Adverse reactions
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	parotid gland enlargement, diarrhoea, 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 category for adverse reactions was similar for the first and second vaccine doses. The exception to this was pain at the injection site which was "Common" after the first vaccine dose and "Very common" after the second vaccine dose.

Post-marketing data

The following 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, 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 symptoms (including transient gait disturbance and transient ataxia), Guillain-Barré syndrome, transverse myelitis, peripheral neuritis
Vascular disorders	Vasculitis
Skin and subcutaneous tissue disorders	Erythema multiforme

Musculoskeletal and connective tissue disorders	Arthralgia, arthritis

* Encephalitis has 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 diseases (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).

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

Cases of overdose (up to 2 times the recommended dose) have been reported during post-marketing surveillance. No adverse events have been associated to the overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Viral vaccine, ATC code J07BD52

Immune response in children 12 months and older
In clinical studies in children aged from 12 months to 2 years PRIORIX has been demonstrated to be highly immunogenic.

Vaccination with a single dose of PRIORIX induced antibodies against measles in 98.1%, against mumps in 94.4% and against rubella in 100% of previously seronegative vaccinees.

Two years after 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 accepted as an indication of protective efficacy. However, some field studies report that the effectiveness against mumps may be lower than the observed seroconversion rates to mumps.

Immune response in children aged 9 to 10 months
A clinical trial enrolled 300 healthy children 9 to 10 months of age at the time of first vaccine dose. Of these 147 subjects 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 dose given 3 months after the first dose were 100% for measles, 99.2% for mumps and 100% for rubella. Therefore a second dose of PRIORIX should be given within three months to provide optimal immune responses.

Adolescents and adults

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

Intramuscular route of administration
A limited number of subjects received PRIORIX intramuscularly in clinical trials. The seroconversion rates to the three components were comparable to those seen after subcutaneous administration.

5.2 Pharmacokinetic properties

An evaluation of pharmacokinetics in vaccines is not necessary.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on general safety studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Solvent:
Water for injections

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.

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

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.

6.5 Nature and contents of container

Powder in vial (Type I glass) with rubber stopper in the following pack sizes: 10 or 100.

0.5 ml of solution in ampoule or pre-filled syringe (Type I glass) with a stopper with or without needles in the following pack sizes: 10 or 100.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and handling

The solvent and the reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspects prior to reconstitution or administration. In the event of either being observed, do not use the solvent or the reconstituted vaccine.

Solvent in ampoule

The vaccine must be 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.

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

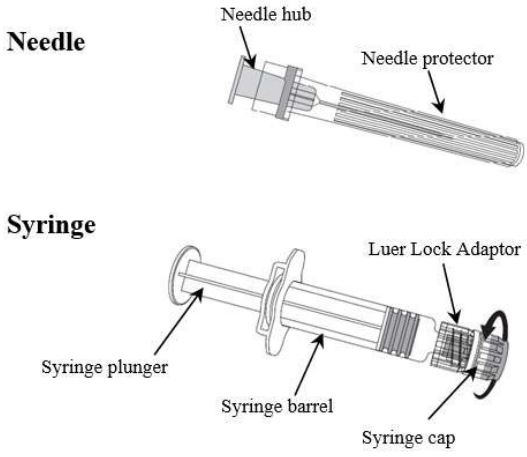
Withdraw the entire contents of the vial.

A new needle should be used to administer the vaccine.

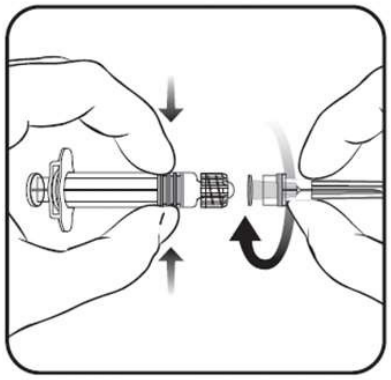
Solvent in pre-filled syringe

The vaccine must be reconstituted by adding the entire contents of the supplied 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 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.

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

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.

Contacts with disinfectants should be avoided (see section 4.4).
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

112-06-29388

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