WHO PRODUCT INFORMATION

NAME OF THE MEDICINAL PRODUCT

Priorix, powder and solvent for solution for injection
Measles, Mumps and Rubella vaccine (live)

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 %

Excipients:
Powder: amino acids (containing phenylalanine), lactose (anhydrous), mannitol (E 421), sorbitol (E 420), medium 199 (containing phenylalanine, para-aminobenzoic acid, sodium and potassium).
Solvent: water for injections

Excipients with known effect:
The vaccine contains 9 mg of sorbitol.
1 dose presentation: The vaccine contains 6.5 nanograms of para-aminobenzoic acid and 334 micrograms of phenylalanine per dose.
2 doses presentation: The vaccine contains 3.25 nanograms of para-aminobenzoic acid and 167 micrograms of phenylalanine per dose.
See section "Special warnings and precautions for use".

Neomycin is present as a residual from the manufacturing process (see section "Contraindications").

Before reconstitution, the powder is a whitish to slightly pink coloured cake, a portion of which may be yellowish to slightly orange.
The solvent is a clear and colourless solution.

CLINICAL PARTICULARS

Therapeutic indications

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

Posology and method of administration

Posology

A single dose (0.5 ml) of the reconstituted vaccine is recommended.

In countries where the incidence and mortality from measles is high in the first year of life, the recommended age for immunization using MMR is at 9 months of age (270 days) or soon after (see also section "Special warnings and precautions for use"). In countries where measles infection occurs later in life (due to sustained high vaccine coverage), the age of immunization

can be moved to 12-15 months. A second opportunity is needed both to increase the chance that every child receives at least one dose of measles-containing vaccine and to increase the proportion of the population that is fully immunized. The second dose of measles-containing vaccine can be given through routine or supplemental activities (see also section "Pharmacodynamic properties").

The safety and efficacy of Priorix in infants under 9 months of age has not been established.

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**,** although it can also be given by intramuscular injection, in the deltoid region or in the anterolateral area of the thigh (see sections "Special warnings and precautions for use" and "Pharmacodynamic properties").

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

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

Contraindications

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

Current or recent immunosuppressive therapy (including high doses of corticosteroids). Priorix is not contraindicated in individuals who are receiving topical or low-dose parenteral corticosteroids (e.g. for asthma prophylaxis or replacement therapy) (see section "Special warnings and precautions for use").

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 "Special warnings and precautions for use").

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

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.

Special warnings and precautions for use

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

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 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 is needed.

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 "Contraindications") 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.
Due to the potential risk of decreased vaccine response and/or disseminated diseases, consideration should be given to the time interval between Priorix vaccination and immunosuppressive therapy (see section "Contraindications").

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 effect
Priorix contains para-aminobenzoic acid. It may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.
The vaccine contains 334 micrograms (1 dose presentation) or 167 micrograms (2 doses presentation) 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'.

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.

Pregnancy and lactation

Fertility

Priorix has not been evaluated in fertility studies.

Pregnancy

Pregnant women should not be vaccinated with Priorix.

Studies have not been conducted with Priorix in pregnant women.

In a review of more than 3 500 susceptible women who were unknowingly in early stages of pregnancy when vaccinated with a rubella-containing vaccine, no cases of congenital rubella syndrome were reported. Subsequent post-marketing surveillance identified congenital rubella syndrome associated with a rubella vaccine strain (Wistar RA 27/3) following inadvertent vaccination of a pregnant woman with a measles, mumps and rubella vaccine.

Foetal damage has not been documented when measles or mumps 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

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 “Contraindications”).

Effects on ability to drive and use machines

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

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 measles, mumps, 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 "Special warnings and precautions for use").

Overdose

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

PHARMACOLOGICAL PROPERTIES

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.

Preclinical safety data

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

PHARMACEUTICAL PARTICULARS

Incompatibilities

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

Shelf life

The expiry date is indicated on the label and packaging.

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.

According to WHO recommendations, once the vaccine has been reconstituted, it should be maintained between +2 °C to +8 °C and protected from the sunlight; the vial must be discarded at the end of each immunisation session or after 6 hours from reconstitution, whichever comes first.

Nature and contents of container

Powder in vial (Type I glass) for 1 dose or 2 doses with rubber stopper.
Solution in ampoule (Type I glass) for 1 dose (0.5 ml) or 2 doses (1 ml).
Pack size of 100.

Special precautions for disposal and other 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.

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.

After reconstitution:
1 dose presentation:
Withdraw the entire contents of the vial. A new needle should be used to administer the vaccine.
2 doses presentation:
When using a multidose vial, each dose of 0.5 ml should be withdrawn using a sterile needle and syringe; precautions should be taken to avoid contamination of the contents. A new needle should be used to administer each individual dose of the vaccine.

Contacts with disinfectants should be avoided (see section “Special warnings and precautions for use”).

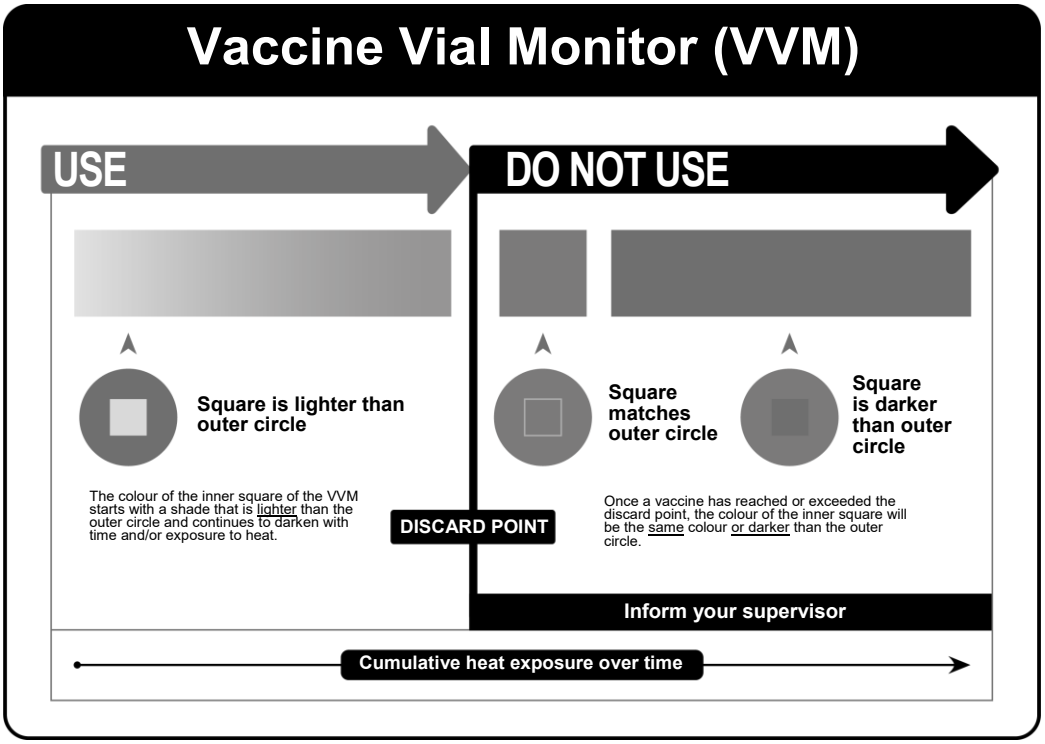
Any unused product or waste material should be disposed of in accordance with local requirements.

Vaccine Vial Monitor (see VVM pictogram at the end of the leaflet)

The Vaccine Vial Monitor (VVM) is part of the cap used for all Priorix batches supplied by GlaxoSmithKline Biologicals. The colour dot that appears on the cap of the vial is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the vial should be discarded.

It is absolutely critical to ensure that the storage conditions specified above (in particular the cold chain) are complied with. GlaxoSmithKline Biologicals will assume no liability in the event Priorix has not been stored in compliance with these storage instructions.



For further information, please contact the manufacturer.

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