**Unit: Technical Assessment Unit**

**Public assessment report for biological products**

***Priorix Vaccine 1 dose & 2 doses***

## Administrative information:

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|---|---|
| Trade name of the medicinal product: | Priorix Vaccine 1 dose & 2 doses |
| INN (or common name) of the active substance(s): | -Live attenuated measles virus, Live attenuated mumps virus and Live attenuated rubella virus |
| Manufacturer of the finished product | FIDIA Farmaceutici S.p.a<br>Via Ponte della Fabbrica, 3/A<br>35031 Abano Terme (Padova)-Italy |
| Marketing Authorization holder | GlaxoSmithKline Biologicals S.A<br>89 Rue de l'institut<br>1330 Rixensart<br>Belgium |
| Applied Indication(s): | -Active immunization against Measles, Mumps and Rubella<br>- Each 0.5 ml contains:<br>Live attenuated measles virus ($\geq 10^{3.0}$ $CCID_{50}$)<br>Live attenuated mumps virus ($\geq 10^{3.7}$ $CCID_{50}$)<br>Live attenuated rubella virus ($\geq 10^{3.0}$ $CCID_{50}$) |
| Pharmaceutical form(s) and strength(s): | -Powder and Solvent for Solution for Injection 0.5 ml |
| Route of administration | IM injection |
| Type of registration (EMA/FDA – Local) | Imported |

## List of abbreviations

| | |
|---|---|
| **EMEA** | European Medicine Evaluation Agency |
| **GCP** | Good Clinical Practice |
| **GLP** | Good Laboratory Practice |
| **HSA** | human serum albumin |
| **IM** | Intramuscular |

| | |
|---|---|
| **MMR** | Measles, Mumps and Rubella |
| **MMRV** | Measles, Mumps, Rubella and Varicella |
| **NOAEL** | no observed adverse effect level |
| **SC** | Subcutaneous |
| **SAEs** | serious adverse events |
| **WHO** | World Health Organization |

**Table of contents**



1. **General introduction about the product including brief description of the AI, its mode of action and indications:**
   - Priorix Vaccine is used for the active immunization against measles, mumps and rubella. The combined measles (M), mumps (M), and rubella (R) vaccine (live) is a freeze-dried preparation presented as 0.5 ml mono-dose or two-dose (two times 0.5 ml after reconstitution) in 3 ml glass vial to be reconstituted with water for injection. The diluent is presented as 0.5 ml mono-dose in glass syringe or glass ampoule, or a 2 ml glass ampoule for the two-dose presentation. The vaccine is presented as a freeze-dried preparation in 3 ml clear glass vial (Type 1, Ph. Eur.). Vials are fitted with bromobutyl rubber stoppers suitable for lyophilisation, aluminium overcaps and flip-off caps.

2. **Quality aspects:**

**2.2.1 Introduction**

As mentioned in the aforementioned section.

**2.2.2 Drug Substance (Active ingredient)**

- **General information**

**Measles Component:**

- **Nomenclature:** Live attenuated measles vaccine, Schwarz strain
- **Structure:** The measles virus is a member of the Morbillivirus genus and belongs to the family of Paramyxoviridae. This relatively large virus is 100 to 300 nm in diameter and roughly spherical in shape.
- **General Properties:** The measles monovalent bulk drug substance is a clarified viral suspension free from intact cells, stabilized in a solution containing sorbitol, amino acids and inorganic salts.

**Mumps Component:**

- **Nomenclature:** Live attenuated mumps vaccine, Jeryl Lynn strain
- **Structure:** The active ingredient is a live attenuated strain of mumps virus, which is classified as a member of the genus Paramyxovirus in the family Paramyxoviridae. Mumps virions are pleiomorphic with particle size ranging from 100 to 600 nm.
- **General Properties:** The mumps monovalent bulk drug substance is a clarified viral suspension free from intact cells, stabilized in a solution containing sorbitol, lactose, amino acids and inorganic salts.

**Rubella Component:**

- **Nomenclature:** Live attenuated rubella vaccine, RA27/3 strain
- **Structure:** The rubella virus, which belongs to the Togavirus family, is a spherical and rather small particle that measures 60-70 nm in diameter. Individual virions consist of a 30-nm electron-dense core surrounded by a lipid envelope.
- **General Properties:** The rubella monovalent bulk drug substance is a clarified viral suspension free from intact MRC5 cells and stabilized in the harvest stabilizer solution containing sorbitol, amino acids and inorganic salts.

- **Manufacture, process controls and characterization:**

**Manufacturer**:

**Manufacturing & testing of the drug substance (measles, mumps & rubella components):**

GlaxoSmithKline Biologicals SA
Parc de la Noire Epine
Rue Fleming, 20
1300 Wavre
Belgium

**Additional manufacturing site for the mumps component:**

GSK Vaccines GmbH
Emil-von-Behring-Str. 200
D-35041 Marburg

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Germany

**Description of Manufacturing Process and Process Controls.**
- Flow diagrams for the bulk production process for measles, mumps and rubella are provided in the MA file.
- A detailed description of the manufacturing process is provided in the MA file.

**Control of Materials.**
- Flow charts for the production process of the working seeds are provided, and control tests are explained in details.
- The passage history of the MCB and the WCB production process are provided in the MA file.
- The quality control testing performed at various stages of the preparation of the vaccine bulk is provided.
- List of the raw materials and chemicals used in the manufacturing process and their specification are described in the MA file.

- **Controls of Critical Steps and Intermediates.**
The production stages subjected to QC testing, the routine test and specifications are provided in the MA file.

**Process Validation**
- The process validation and evaluation performed on the drug substances manufacturing process is provided in the MA file to demonstrate that the process consistently yields a product which reliably meets specifications.

- **Manufacturing Process Development.**
- The manufacturing process of the measles, mumps and rubella monovalent bulks is routinely applied for commercial vaccine bulk production and is a classical manufacturing process based on the Ph. Eur. requirements and WHO.

- **Characterization.**
The impurities that could be found in the monovalent bulks are process-related only.

- **Specification**
The specifications related to the release testing of the measles, mumps and rubella bulks are provided in the MA file.

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- **Reference Standards or Materials.**
  Details regarding the reference standards are provided in the MA file.

- **Container closure system**
  - The containers used for storing the bulks are listed and information about each container is provided in the MA file.
  - Compatibility between bulk vaccines and primary container/closure materials is demonstrated.

- **Stability of drug substance**

- Recommended storage condition: -45°C.
- Shelf-life: 72 months

**2.2.3 Drug product:**

- **Description and Composition of the Drug Product:**

- **One dose:** The combined measles (M), mumps (M), and rubella (R) vaccine (live) is a freeze-dried preparation presented as 0.5 ml monodose in 3 ml glass vial to be reconstituted with water for injection. The diluent is presented as 0.5 ml monodose in glass syringe or glass ampoule.

**Two doses:** The combined measles (M), mumps (M), and rubella (R) vaccine (live) is a freeze-dried preparation presented as a two-dose (two times 0.5 ml after reconstitution) vaccine in 3 ml glass vial to be reconstituted with water for injection. The Water for Injection diluent is presented in a 2 ml glass ampoule.

- The active substances are live attenuated measles, mumps and rubella viruses. The excipients include anhydrous lactose, sorbitol, mannitol, amino acids and water for injection.
- The vaccine is presented as a freeze-dried preparation in 3 ml clear glass vial (Type 1, Ph. Eur.). Vials are fitted with bromobutyl rubber stoppers suitable for lyophilisation, aluminium overcaps and flip-off caps.

**- Pharmaceutical Development including brief description on Components of drug product.**

- The development of the candidate vaccine measles, mumps and rubella vaccine was centered only on the mumps active ingredient, as the measles and rubella ingredients and the excipients are the same as those used in the previous licensed Company's measles, mumps and rubella vaccine which was marketed world-wide.

**- Formulation Development**

The amount of live attenuated measles, mumps and rubella virus in the MMR vaccine conforms to the WHO (TRS N° 840, 1994) and Ph. Eur. (N° 1057) recommendations. The immunogenicity and tolerability of the vaccine has been demonstrated in clinical trials.

**- Manufacturing Process Development**
- The Company has first developed a mono-dose trivalent MMR vaccine and, afterwards, based on the manufacturing experience built on this mono-dose presentation, has developed a two-dose presentation.
- A flow chart for both presentations is presented in the MA file.

- **Microbiological Attributes.**
- The vaccine is a sterile preservative-free vaccine.
- At the end of the lyophilisation process, sterile dry nitrogen is introduced in each container prior to complete insertion of the stopper. The integrity of the container closure system was demonstrated for the lots included in the stability studies up to 24 months of storage.

**- Compatibility.**
The solution is free from visible particles. It is recommended to inject the vaccine promptly after reconstitution. However, the stability at +2°C to +8°C has been demonstrated for 24 hours after reconstitution. The compatibility of the vaccine with the diluent is thus satisfactory.

**Manufacture of the drug product:**
**- Description of manufacturing process and process controls along with manufacturers and responsibilities**
**Manufacturer:**
**- Formulation of the MMR vaccine, filling and lyophilization are performed at:**
FIDIA Farmaceutici S.p.a.
Via Ponte della Fabbrica,3/A
35031 Abano Terme (Padova)
Italy
- A flow diagram of the vaccine manufacturing process is provided in the MA file.

- **Product specification:**
  - The specifications for the release of the MMR vaccine are described in the MA file.

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- The reference for the analytical procedures used for release testing of the MMR final bulk and final container vaccine are presented and all in-house analytical procedures are described in the MA file.
- The vaccine is tested in compliance with the WHO and Ph. Eur. requirements for combined measles, mumps and rubella live attenuated vaccine. The validation data for the analytical procedures developed in-house are provided.

- **Reference Standards or Materials.**
  Details regarding the reference standards are provided in the MA file.

- **Container closure system.**
  - The formulation is filled and lyophilised in 3 ml vial containers, sealed with 13 mm ready to sterilise (RTS) stoppers for lyophilised formulations and secured with flip-off caps.
  - For each container closure system component, a description and the corresponding specifications are provided.

- **Stability of the drug product.**
  -Based on available stability data:
  **Approved Shelf Life**: 24 months
  **Approved Storage Conditions**: 2-8º

- **Adventitious agents:**
  The working seeds and cell banks are tested for the following:
  - Bacteria, mycoplasma and fungi
  - Transmissible Spongiform Encephalopathy agents
  - Viral adventitious agents

## 3. Non-clinical aspect

Measles, Mumps and Rubella (MMR) vaccine Priorix is a lyophilised mixed preparation of the attenuated Schwarz measles, RIT 4385 mumps (Jeryl Lynn derived strain) and Wistar RA 27/3 rubella strains of viruses, separately obtained by propagation either in chick embryo tissue cultures (mumps and measles) or MRC5 human diploid cells (rubella).
Priorix vaccine was first registered in Europe in November 1997, before the EMEA Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines came into force in 1998. Furthermore, none of the active ingredients or excipients in Priorix vaccine are novel. Consequently, GLP toxicity studies were not performed with Priorix vaccine. However,

tests for the measles, mumps and rubella working seeds have been conducted in animals, including: neurovirulence test in monkeys, extraneous agents test in suckling mice, adult mice and guinea pigs. Furthermore, general safety tests in mice and guinea pigs have been performed on production lots of the final combined vaccine in accordance with the WHO requirements.
In addition, the effects of single or repeated subcutaneous injection of GSK's Measles, Mumps, Rubella and Varicella (MMRV) vaccine Priorix-Tetra have been evaluated in a pivotal GLP toxicity study in the Rhesus monkeys. It should be noted that the MMR bulks used to formulate GSK's MMR and MMRV vaccines are the same. With respect to the excipient, Priorix-Tetra contains the same excipient levels as Priorix. Thus, it is deemed acceptable that the GLP toxicity study with Priorix-Tetra is also applicable for the nonclinical safety evaluation of Priorix.

**Pharmacology**
MMR combination includes three distinct viruses, each having its own host specificity. Consequently, a common host that allows replication of all viruses and which could serve as a relevant animal model for testing the combined vaccine for toxicity is not currently available. Considering the sensitivity of various laboratory animal species, the Rhesus monkey was selected as the most appropriate species to use for immunogenicity and toxicity testing. Rhesus monkeys have been reported to be a good model for Measles virus infection and will support replication of Mumps and Rubella.
Administration of the Priorix-Tetra vaccine resulted in 100% seroconversion to Rubella virus while all saline recipients were seronegative.
Furthermore, 100% seroconversion was also demonstrated for Varicella, although 2 out of 8 monkeys had positive pre-immunisation values. For Mumps, the seroconversion rate was low (1 out of 8 monkeys) and, for Measles, there was an unexpected pre-existing immunity.

**Pharmacokinetic studies:** No pharmacokinetic studies were performed in accordance with the Note for Guidance on Preclinical Pharmacological and Toxicological testing of vaccines (CPMP/465/95).

**Toxicology:**
The effects of single or repeated subcutaneous injection of Priorix-Tetra were evaluated in a GLP-compliant toxicity study in Rhesus monkeys. The subcutaneous route of administration was used since that is the intended route of human administration. Animals weighing approximately 4.0-5.0 kg were used in the study. The full human dose (0.5 ml/injection) containing either saline (control) or Priorix-Tetra was administered subcutaneously.
Results demonstrated that single or multiple subcutaneous injections of Priorix-Tetra were well

tolerated in the Rhesus monkey. No treatment-related toxic effects were observed on clinical signs, body weight evolution, food consumption, hematology, clinical chemistry, body temperature, ophthalmoscopy, electrocardiography, blood pressure, organ weights, macroscopic or microscopic examinations. Based on these results, single or repeated SC injection of the full human dose of Priorix-Tetra in Rhesus monkeys was considered the no observed adverse effect level (NOAEL).

## 4. Clinical aspect

- **Clinical Overview**

  Priorix is a live attenuated measles, mumps, and rubella (MMR) vaccine developed for active immunization against measles, mumps, and rubella. The clinical development program comprised more than 40 clinical studies involving over 14,000 subjects aged approximately 8 months to 16 years. Clinical studies were conducted in accordance with Good Clinical Practice (GCP) guidelines and evaluated Priorix when administered as a single-dose primary vaccination, a two-dose primary vaccination schedule, or as a second dose following previous measles-containing vaccination.

  The clinical program included assessments of immunogenicity, antibody persistence, manufacturing consistency, formulation comparability, co-administration with other pediatric vaccines, and safety across different age groups and vaccination schedules. Comparisons were performed with licensed MMR vaccines, primarily M-M-R II/MMRVax, which have demonstrated established effectiveness in routine immunization programs.

  The available clinical evidence demonstrates that Priorix induces robust immune responses against measles, mumps, and rubella, provides durable antibody persistence, and exhibits a favorable safety profile consistent with that expected for live attenuated MMR vaccines.

- **Clinical Efficacy**

  Direct placebo-controlled efficacy studies were not conducted because routine MMR vaccination programs have substantially reduced the incidence of measles, mumps, and rubella, making such studies both impractical and ethically inappropriate. Consequently, vaccine efficacy has been established through immunogenicity assessments and comparisons with licensed MMR vaccines with proven field effectiveness.

  Clinical studies demonstrated that Priorix:

• Induces strong immune responses following a single dose administered during the second year of life.
• Maintains antibody persistence for at least two years following a single dose.
• Is immunogenic when administered to infants younger than 12 months of age and may be used in situations where early protection against measles is required.
• Can be administered from 9 months of age in measles-endemic settings or during outbreaks; however, a second dose is recommended to achieve optimal seroconversion rates and long-term protection.
• Produces enhanced immune responses and higher antibody concentrations when administered as a two-dose schedule, with persistence demonstrated for at least three years.
• Can be administered safely and effectively as a second dose in children previously vaccinated with a measles-containing vaccine.
• Can be administered following prior monovalent measles vaccination.
• Can be co-administered with varicella vaccine and other routinely administered childhood vaccines without clinically relevant interference with immune responses.
The immune response induced by Priorix was demonstrated to be non-inferior to that induced by M-M-R II/MMRVax, supporting comparable clinical effectiveness for the prevention of measles, mumps, and rubella.

- **Clinical Immunogenicity**

Immunogenicity was assessed using validated serological assays measuring antibodies against measles, mumps, and rubella. Blood samples were generally collected before vaccination and approximately six weeks after vaccine administration.

The currently marketed human serum albumin (HSA)-free formulation of Priorix demonstrated robust immune responses in children aged 12–24 months.

Following a single dose, pooled seroconversion rates at six weeks were:

• Measles: 98.1%
• Mumps: 94.4%
• Rubella: 100.0%

The HSA-free formulation demonstrated immunogenicity comparable to the previous HSA-containing formulation and met predefined non-inferiority criteria for all three antigens. Comparable immune responses were also observed when Priorix was compared with M-M-R II.

Persistence studies demonstrated sustained immunity. Two years after vaccination, seropositivity rates remained high for all antigens, ranging from approximately 92% to 100%. Antibody concentrations remained above predefined seropositivity thresholds, supporting durable immune protection.

Additional clinical studies demonstrated:

• Consistent immunogenicity across three commercial production lots.
• Maintenance of immune responses following storage of the vaccine for up to three years at 2-8°C according to recommended storage conditions.
• Enhanced immune responses and higher geometric mean antibody titers following administration of a second dose.
Collectively, the immunogenicity data demonstrate that Priorix induces strong, consistent, and persistent immune responses against measles, mumps, and rubella across approved vaccination schedules.

- **Clinical Safety**

The safety profile of Priorix was evaluated in 37 clinical studies involving more than 12,000 subjects who received Priorix without concomitant vaccination.

Safety assessments included solicited local and systemic adverse events, unsolicited adverse events, serious adverse events (SAEs), and long-term follow-up.

Common Adverse Events

The most frequently reported local adverse events were redness, pain, and swelling at the injection site.
Among subjects receiving Priorix as a first dose:
• Redness: 10.9%
• Pain: 4.5%
• Swelling: 4.1%
Among subjects receiving Priorix as a second dose:
• Redness: 19.0%
• Pain: 11.1%
• Swelling: 6.6%
Fever was the most frequently reported systemic adverse event.
Following the first dose:
• Fever ≥38.0°C: 24.3%
• Fever ≥39.5°C: 3.6%

Following the second dose:
• Fever ≥38.0°C: 14.9%
• Fever ≥39.5°C: 1.9%
A transient increase in fever incidence was observed between Days 4 and 11 following the first dose, reflecting replication of the attenuated measles vaccine virus. This is a recognized characteristic of live attenuated viral vaccines.
Other solicited adverse events considered at least possibly related to vaccination included:
First dose:
• Rash: 5.1%
• Parotid gland swelling: 0.4%
• Signs of meningism, including febrile convulsions: 0.02%
Second dose:
• Rash: 2.3%
• Parotid gland swelling: 0.3%
• Signs of meningism: 0%
Febrile convulsions were reported only rarely.
Serious Adverse Events
A total of 88 serious adverse events were reported among Priorix recipients. Ten events were considered by investigators to be at least possibly related to vaccination. Most subjects recovered completely.
One death occurred during clinical development; comprehensive investigation concluded that the event was unrelated to vaccination.
Only a small number of subjects discontinued participation because of adverse events or serious adverse events.
Unsolicited Adverse Events
The most commonly reported unsolicited adverse events included vomiting, rhinitis, pharyngitis, upper respiratory tract infection, diarrhea, cough, nervousness, and injection-site reactions. These events were generally mild, transient, and consistent with the known safety profile of MMR vaccines.
***Post-Marketing Experience**
Priorix was first approved in 1997 and is licensed in approximately 100 countries worldwide. As of August 2010, more than 234 million doses had been distributed globally. Post-marketing surveillance data have remained consistent with findings from clinical studies. Pyrexia and rash were the most frequently reported post-marketing adverse events. Very rare events such as thrombocytopenia and Guillain–Barré syndrome have been reported in association with MMR vaccination and are reflected in the product information as part of routine pharmacovigilance activities.

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No new safety concerns have been identified from post-marketing experience.

- **Benefit-Risk Assessment**

Measles, mumps, and rubella remain important vaccine-preventable diseases. The World Health Organization (WHO) supports the use of combined MMR vaccines as an effective strategy to reduce disease burden and contribute to measles and rubella elimination efforts.

Combination vaccines offer important public health advantages by reducing the number of injections and healthcare visits, simplifying vaccination schedules, improving compliance, and reducing the potential for administration errors.

The clinical development program demonstrated that Priorix is highly immunogenic and capable of inducing durable immune responses against measles, mumps, and rubella. The vaccine has demonstrated non-inferiority to licensed MMR vaccines with established effectiveness and has shown suitability for use in routine immunization schedules, including administration as a second dose and in situations where early protection is required.

The safety profile of Priorix is well characterized and supported by both clinical studies and extensive post-marketing experience involving more than 234 million distributed doses worldwide. Reported adverse events were generally mild and transient, and no new safety concerns have emerged during routine pharmacovigilance monitoring.

Considering the demonstrated protection against measles, mumps, and rubella, the durability of immune responses, the flexibility of administration schedules, and the favorable safety profile, the benefits of Priorix substantially outweigh the identified and potential risks.

- **Clinical Conclusion**

The clinical development program and extensive post-marketing experience provide comprehensive evidence supporting the safety, immunogenicity, and effectiveness of Priorix. Priorix has been shown to induce robust immune responses against measles, mumps, and rubella across a broad age range and vaccination schedules, including single-dose and two-dose regimens. The vaccine demonstrated non-inferiority to established MMR vaccines, durable antibody persistence, manufacturing consistency, and compatibility with concomitant administration of other routine childhood vaccines.
The vaccine is generally well tolerated, with a safety profile consistent with that expected for live attenuated MMR vaccines. Clinical safety findings have been confirmed through global post-marketing experience involving more than 234 million distributed doses.

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Overall, the available evidence supports a positive benefit–risk balance for Priorix. The vaccine represents a safe, effective, and convenient strategy for the prevention of measles, mumps, and rubella and contributes to ongoing national and global disease control and elimination efforts.

**5. General Conclusion and Recommendations if any:**

Based on the review of CTD modules and other supplementary documents, the product is approved.

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