NEW DRUG APPROVAL

Brand Name	Priorix
Generic Name	measles, mumps and rubella vaccine, live
Drug Manufacturer	GlaxoSmithKline Biologicals SA

New Drug Approval

FDA Approval Date: June 6, 2022

Review Designation: N/A

Review Type: Biologic License Application (BLA): 125748

Dispensing Restrictions: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Measles:

Measles is a highly contagious viral illness that occurs worldwide. The infection is characterized by fever, malaise, cough, coryza, and conjunctivitis, followed by exanthem. Following exposure, approximately 90 percent of susceptible individuals will develop measles. The period of contagiousness is estimated to be from five days before the appearance of the rash to four days afterward. The illness may be transmitted in public spaces, even in the absence of person-to-person contact.

Measles is a highly contagious viral illness characterized by fever, malaise, rash, cough, coryza, and conjunctivitis. Measles has been targeted for eradication given the favourable biologic characteristic that humans are the only reservoir; however, due to social and political factors and high transmissibility, elimination has been achieved in very few areas of the world. Measles occurs worldwide and remains a leading cause of mortality especially among children ≤5 years of age. Precise worldwide incidence estimates are difficult to obtain because of heterogeneous surveillance systems and probable under-reporting. Measles occurs predominantly in areas with low vaccination rates, particularly resource-limited settings. However, even in resource-rich settings, outbreaks of measles have occurred in settings where vaccination uptake has declined.

Mumps:

Mumps is a contagious viral illness that is largely preventable via vaccination. Typically, it begins with a few days of fever, headache, myalgia, fatigue, and anorexia, followed by parotitis; the illness is usually self-limited.

Mumps occurs worldwide; the peak incidence is typically in the late winter to early spring, although sporadic outbreaks occur at any time of year. Mumps occurs most commonly among school-aged children and college-aged young adults; it is rare among infants less than one year of age, who have protection via maternal antibodies.

Before the United States mumps vaccination program began in 1967, about 186,000 cases were reported each year; the actual number of cases was likely much higher due to underreporting. Since implementation of routine vaccination, there has been a more than 99 percent decrease in mumps cases in the United States. From year to year in the United States, mumps cases can range from a few hundred to a few thousand. The number of cases reported in 2016 and 2017 (6369 and 5629, respectively) were the highest in a decade.

Rubella:

Rubella is a viral illness that most often presents as a self-limiting illness in children but can have devastating effects on the fetus when acquired during pregnancy. It was first described in the 1750s and is often referred to as "German measles" due to its characteristic rash that is similar to measles and the attention it received in German literature.

In 2004, rubella was officially declared eliminated from the United States; in 2015, rubella was eliminated from the Americas. The region of the Americas has sustained elimination of rubella and congenital rubella syndrome. As of July 2020, 173 of 195 countries (89 percent) had introduced rubella vaccines into immunization programs, with 84 (43 percent) of countries eliminating transmission of rubella.Despite this progress, rubella cases continue to occur, with 14,621 cases occurring globally in 2018.

Efficacy

The effectiveness of Priorix is based on a comparison of antibody responses relative to M-M-R II. Antibody responses to measles, mumps, and rubella viruses were measured by ELISAs. Analyses evaluated antibody geometric mean concentrations (GMC) and seroresponse rates (SRR). Seroresponse thresholds are 200 mIU/mL, 10 ELU/mL, and 10 IU/mL for anti-measles virus, anti-mumps virus, and anti-rubella virus antibodies, respectively.

Antibody Responses to Measles, Mumps and Rubella Viruses

Children 12 through 15 Months of Age Who Received Priorix as a First Dose

In Study 1 (NCT01702428), 5,003 participants 12 through 15 months of age received a first dose of Priorix (n = 3,714) or M-M-R II (n = 1,289) Antibody responses to measles, mumps, and rubella viruses were measured by ELISAs using sera obtained 42 days following the first dose of either Priorix or M-M-R II. Non-inferiority of the immune response after the first dose of Priorix compared with M-M-R II was demonstrated in terms of SRR and GMC to measles, mumps, and rubella viruses. The immune responses measured in the U.S. study participants were similar to those in the overall study population. A summary of immune responses is shown in table 1.

Table 1. Immune Responses after the First Dose of Priorix Compared with M-M-R II (Study 1, NCT01702428, According-to-Protocol Population)

Parameter	Virus Antigen	Priorix N = 3,187-3,248	M-M-R II N = 1,107-1,137	Difference (Priorix minus M-M-R II) (95% CI)
SRR[a] (%)	Measles	98	98	0.18 (-0.68, 1.25)
	Mumps	98	98	0.81 (-0.10, 1.96)
	Rubella	97	99	-1.15 (-2.00, -0.15)
		Priorix N = 3,187-3,248	**M-M-R II N = 1,107-1,137**	**Ratio (Priorix/M-M-R II) (95% CI)**
GMC[b]	Measles (mIU/mL)	3,165	3,215	0.98 (0.93, 1.05)
	Mumps (ELU/mL)	76	73	1.05 (0.99, 1.11)

	Rubella (IU/mL)	53	60	0.87 (0.83, 0.92)

According-to-Protocol cohort included all vaccinated participants who met protocol-defined criteria for immunogenicity analysis.

Priorix or M-M-R II was administered concomitantly with Havrix and Varivax; U.S. participants also received Prevnar 13.
N = Number of participants.
SRR = Seroresponse rate (percentage of initially seronegative participants with concentration above seroresponse threshold for each assay).
GMC = Geometric mean antibody concentration adjusted for country.
CI = Confidence Interval
[a] Non-inferiority criterion met for all antigens (lower limit of 2-sided 95% CI for the difference [group receiving Priorix minus group receiving M-M-R II] was ≥-5%).
[b] Non-inferiority criterion met for all antigens (lower limit of 2-sided 95% CI for the ratio [group receiving Priorix over group receiving M-M-R II] was ≥0.67).

Children 12 through 15 Months of Age Who Received a Second Dose of Priorix 6 Weeks after the First Dose
In Study 2 (NCT01681992), 4,516 participants 12 through 15 months of age received a first dose of Priorix (n = 2,990) or M-M-R II (n = 1,526) followed by a second dose of the same vaccine 6 weeks later. Antibody responses to measles, mumps, and rubella viruses were measured in a subset of participants (n = 199 – 259 Priorix; n = 212 – 257 M-M-R II) in sera obtained 42 days following the second dose of either Priorix or M-M-R II. In a descriptive analysis, the immune response after a second dose was similar between the group receiving Priorix and the group receiving M-M-R II in terms of antibody SRR and GMC for all antigens.

Children 4 through 6 Years of Age Who Received Priorix as a Second Dose of Measles, Mumps, and Rubella Virus Vaccine.
In Study 3 (NCT01621802), 4,007 participants 4 through 6 years of age received Priorix (n = 2,917) or M-M-R II (n = 1,090) as a second dose following administration of an initial dose of a combined measles, mumps, and rubella virus-containing vaccine in the second year of life. Prior to vaccination, the percentages of participants with antibody levels above the seroresponse thresholds were 98.0% for measles, 95.7% for mumps, and 98.7% for rubella. Antibody responses to measles, mumps, and rubella viruses were measured by ELISAs using sera obtained 42 days following of either Priorix or M-M-R II as a second dose. The non-inferiority of Priorix to M-M-R II when administered with Kinrix and Varivax was demonstrated in terms of SRR and GMC to measles, mumps, and rubella viruses at Day 42.

Table 2. Immune Responses to Priorix Compared with M-M-R II as a Second Dose in Children 4 through 6 Years of Age (Study 3, NCT01621802, According-to-Protocol Population)

Parameter	Virus Antigen	Priorix N = 690-698	M-M-R II N = 245-250	Difference (Priorix minus M-M-R II) (97.5% CI)
SRR[a] (%)	Measles	100	100	0.00 (-0.72, 1.98)
	Mumps	100	100	0.00 (-0.72, 1.97)
	Rubella	100	100	-0.14 (-0.98, 1.84)
		Priorix	**M-M-R II**	**Ratio**

		N = 690-691	N = 245-248	(Priorix/M-M-R II) (97.5% CI)
GMC[b]	Measles (mIU/mL)	4,285	4,333	0.99 (0.92, 1.06)
	Mumps (ELU/mL)	171	188	0.91 (0.83, 1.00)
	Rubella (IU/mL)	97	94	1.03 (0.97, 1.09)

According-to-Protocol cohort included all vaccinated participants who met protocol-defined criteria for immunogenicity analysis.

N = Number of participants.
SRR = Seroresponse rate (percentage of participants with concentration above seroresponse threshold for each assay).
GMC = Geometric mean antibody concentration adjusted for pre-vaccination concentration.
CI = Confidence Interval.
a Non-inferiority criterion met for all antigens (lower limit of 2-sided 97.5% CI for the difference [group receiving Priorix minus group receiving M-M-R II] was ≥-5%).
b Non-inferiority criterion met for all antigens (lower limit of 2-sided 97.5% CI for the ratio [group receiving Priorix over group receiving M-M-R II] was ≥0.67).

Individuals 7 Years of Age and Older Who Received Priorix as a Second Dose of Measles, Mumps, and Rubella Vaccine

In Study 4 (NCT02058563), 860 participants 7 years of age and older received Priorix (n = 426) or M-M-R II (n = 434) as a second dose following previous administration of a combined measles, mumps, and rubella virus-containing vaccine. Prior to vaccination, the percentages of participants with antibody levels above the seroresponse thresholds were 93.1% for measles, 88.0% for mumps, and 81.9% for rubella. Antibody responses to measles, mumps, and rubella viruses were measured in sera obtained 42 days following the second dose of either Priorix or M-M-R II. The non-inferiority of the immune response after the second dose of Priorix compared with M-M-R II was demonstrated in terms of SRR and antibody GMC to measles, mumps, and rubella antigens.
A summary of immune responses is shown in Table 3.

Table 3. Immune Responses to Priorix as a Second Dose Compared with M-M-R II (Study 4, NCT02058563, According-to-Protocol Population)

Parameter	Virus Antigen	Priorix N = 405	M-M-R II N = 414	Difference (Priorix minus M-M-R II) (95% CI)
SRR[a] (%)	Measles	99	99	-0.51 (-2.22, 1.02)
	Mumps	98	100	-1.25 (-3.10, 0.23)
	Rubella	100	100	-0.25 (-1.57, 0.90)
		Priorix N = 404	**M-M-R II N = 413**	**Ratio (Priorix/M-M-R II) (95% CI)**

GMC[b]	Measles (mIU/mL)	1,754	1,783	0.98 (0.89, 1.09)
	Mumps (ELU/mL)	114	110	1.04 (0.94, 1.15)
	Rubella (IU/mL)	76	74	1.03 (0.94, 1.12)

According-to-Protocol cohort included all vaccinated participants who met protocol-defined criteria for immunogenicity analysis.

N = Number of participants.
SRR = Seroresponse rate (percentage of participants with concentration above seroresponse threshold for each assay).
GMC = Geometric mean antibody concentration adjusted for gender, age, country, and pre-vaccination concentration.
CI = Confidence Intervals.
a Non-inferiority criterion met for all antigens (lower limit of 2-sided 95% CI for the difference [group receiving Priorix minus group receiving M-M-R II] was ≥-5%).
b Non-inferiority criterion met for all antigens (lower limit of 2-sided 95% CI for the ratio [group receiving Priorix over group receiving M-M-R II] was ≥0.67).

Concomitant Administration:

Concomitant Administration with Havrix, Varivax, and Prevnar 13

The concomitant use of Priorix or M-M-R II with Havrix and Varivax was evaluated in Study 1 (NCT01702428) in children 12 through 15 months of age. All participants received Priorix or M-M-R II administered concomitantly with Havrix and Varivax. Children enrolled in the U.S. also received Prevnar 13 concomitantly.

In subsets of participants in Study 1, immune responses to the antigens contained in Havrix, Varivax, and Prevnar 13 were measured in sera obtained 42 days after concomitant administration of Priorix or M-M-R II. There was no evidence that Priorix interfered with the antibody responses to these vaccines relative to the antibody responses when M-M-R II was concomitantly administered.

Concomitant Administration with Kinrix and Varivax

The concomitant use of Priorix or M-M-R II with Kinrix and Varivax was evaluated in Study 3 (NCT01621802) in children 4 through 6 years of age. A subset of participants received Priorix or M-M-R II administered concomitantly with Kinrix and Varivax.

Immune responses to the antigens contained in Kinrix and Varivax were measured in sera obtained 42 days after concomitant administration of Priorix or M-M-R II. There was no evidence that Priorix interfered with the antibody responses to these vaccines relative to the antibody responses when M-M-R II was concomitantly administered.

Safety

ADVERSE EVENTS

Most common solicited adverse reactions in clinical trials participants:

- 12 through 15 months of age: local reactions were pain (26%) and redness (25%); systemic reactions were irritability (63%), loss of appetite (45%), drowsiness (45%), and fever (35%).
- 4 through 6 years of age: local reactions were pain (41%), redness (22%), and swelling (11%); systemic reactions were loss of appetite (21%), drowsiness (27%), and fever (24%).
- 7 years of age and older: local reactions were pain (12%) and redness (12%).

WARNINGS & PRECAUTIONS

- There is a risk of febrile seizure following administration of Priorix.
- Thrombocytopenia and thrombocytopenic purpura have been reported following vaccination with Priorix
- Syncope (fainting) can occur in association with administration of injectable vaccines, including Priorix. Procedures should be in place to avoid injury from fainting.
- The tip caps of the prefilled syringes contain natural rubber latex, which may cause allergic reactions.

CONTRAINDICATIONS

- **Severe Allergic Reactions:** Do not administer Priorix to individuals with a history of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine or after a previous dose of any measles, mumps, and rubella virus-containing vaccine.
- **Immunosuppression:** Due to the risk of disseminated vaccine virus infection, do not administer Priorix to individuals with severe humoral or cellular (primary or acquired) immunodeficiency.
- **Pregnancy:** Do not administer Priorix to individuals who are pregnant. Pregnancy should be avoided for 1 month after vaccination.

Clinical Pharmacology

MECHANISMS OF ACTION

Humoral immune responses against measles, mumps, and rubella viruses induced by Priorix were measured by enzyme-linked immunosorbent assays (ELISAs). IgG antibodies measured by the ELISAs used in clinical studies of Priorix have been shown to correlate with the presence of neutralizing antibodies that have been associated with protection.

Dose & Administration

ADULTS

None

PEDIATRICS

After reconstitution, a single dose of Priorix is approximately 0.5 mL. Administer according to the following schedule:

- The first dose is administered at 12 through 15 months of age.
- The second dose is administered at 4 through 6 years of age.

GERIATRICS

None

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

NEW DRUG APPROVAL

Priorix is a suspension for injection supplied as a single-dose vial of lyophilized antigen component to be reconstituted with the accompanying prefilled syringe of sterile water diluent component. A single dose after reconstitution is approximately 0.5 mL.