

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ERVEBO safely and effectively. See full prescribing information for ERVEBO.

ERVEBO® (Ebola Zaire Vaccine, Live) Suspension for intramuscular injection
Initial U.S. Approval: 2019

-----RECENT MAJOR CHANGES-----

Indications and Usage (1) 07/2023

-----INDICATIONS AND USAGE-----

ERVEBO® is a vaccine indicated for the prevention of disease caused by *Zaire ebolavirus* in individuals 12 months of age and older. (1)

Limitations of Use (1.1)

- The duration of protection conferred by ERVEBO is unknown.
- ERVEBO does not protect against other species of *Ebolavirus* or *Marburgvirus*.
- Effectiveness of the vaccine when administered concurrently with antiviral medication, immune globulin (IG), and/or blood or plasma transfusions is unknown.

-----DOSAGE AND ADMINISTRATION-----

- Administer a single 1 mL dose of ERVEBO intramuscularly. (2.1)

-----DOSAGE FORMS AND STRENGTHS-----

- 1 mL suspension for injection supplied as a single-dose vial. (3)

-----CONTRAINDICATIONS-----

- Severe allergic reaction (e.g., anaphylaxis) to any component of ERVEBO. (4)

-----WARNINGS AND PRECAUTIONS-----

- Anaphylaxis has been observed following administration of ERVEBO. Appropriate medical treatment and supervision must be available in case of anaphylactic event following the administration of ERVEBO. (5.1)
- Vaccinated individuals should continue to adhere to infection control practices to prevent *Zaire ebolavirus* infection and transmission. (5.2)

- Vaccine virus RNA has been detected in blood, saliva, urine, and fluid from skin vesicles of vaccinated individuals; transmission of vaccine virus is a theoretical possibility. (5.4)

-----ADVERSE REACTIONS-----

The most commonly reported local and systemic adverse events in clinical trials were:

- Individuals 18 years of age and older: injection-site pain (70%); headache (55%); feverishness (39%); muscle pain (33%); somnolence, reduced activity, fatigue (26%); joint pain, arthralgia (19%); chills (17%); injection-site swelling (17%); decreased appetite (15%); abdominal pain (13%); injection-site redness (12%); nausea (10%); arthritis (5%); vomiting (4%), rash (4%); abnormal sweating (3%) and mouth ulceration (2%). (6.1)
- Individuals 12 months through 2 years of age: feverishness (83%); crying (31%); decreased appetite (27%); injection-site pain (26%); somnolence, reduced activity, fatigue (20%); diarrhea (19%); vomiting (17%); irritability (11%); screaming (10%); mouth ulceration (6%); chills (5%); injection-site swelling (5%); headache (4%); abdominal pain (2%); abnormal sweating (2%) and injection-site erythema (1%). (6.1)
- Individuals 3 years through 11 years of age: feverishness (65%); headache (50%); injection-site pain (40%); decreased appetite (24%); somnolence, reduced activity, fatigue (22%); abdominal pain (21%); chills (14%); myalgia (12%); vomiting (11%); dizziness (8%); nausea (8%); injection-site pruritus (7%); crying (3%); arthralgia (3%); diarrhea (3%); injection-site swelling (3%); abnormal sweating (1%); mouth ulceration (2%) and irritability (1%). (6.1)
- Individuals 12 years through 17 years of age: headache (59%); injection-site pain (52%); feverishness (48%); myalgia (30%); somnolence, reduced activity, fatigue (28%); decreased appetite (21%); chills (19%); dizziness (17%); abdominal pain (16%); arthralgia (16%); nausea (8%); abnormal sweating (5%); diarrhea (4%); vomiting (4%); injection-site pruritus (3%); injection-site swelling (3%) and mouth ulceration (2%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme LLC at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2023

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ERVEBO® is indicated for the prevention of disease caused by *Zaire ebolavirus* in individuals 12 months of age and older.

1.1 Limitations of Use

- The duration of protection conferred by ERVEBO is unknown.
- ERVEBO does not protect against other species of *Ebolavirus* or *Marburgvirus*.
- Effectiveness of the vaccine when administered concurrently with antiviral medication, immune globulin (IG), and/or blood or plasma transfusions is unknown.

2 DOSAGE AND ADMINISTRATION

FOR INTRAMUSCULAR ADMINISTRATION ONLY.

2.1 Dosage

Administer 1 mL dose of ERVEBO.

2.2 Preparation

Thaw vial at room temperature until no visible ice is present. Do not thaw the vial in a refrigerator. Gently invert vial several times. The vaccine is a colorless to slightly brownish-yellow liquid with no particulates visible. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exist, discard the vial.

Use the vaccine immediately after thawing. If not used immediately, the vaccine may be stored for 4 hours at room temperature (up to 25°C; 77°F) protected from light. DO NOT REFREEZE [see *How Supplied/Storage and Handling (16)*].

Withdraw the 1 mL dose of vaccine from the vial using a sterile needle and sterile syringe.

2.3 Administration

Administer a 1 mL dose of ERVEBO intramuscularly and discard unused portion.

3 DOSAGE FORMS AND STRENGTHS

ERVEBO is a suspension for injection supplied as a 1 mL dose in single-dose vials.

4 CONTRAINDICATIONS

Do not administer ERVEBO to individuals with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine, including rice protein [see *Description (11)*].

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Among 18,616 participants vaccinated with at least one dose of ERVEBO in clinical trials, there were two reports of anaphylaxis [see *Adverse Reactions (6.1)*]. Monitor individuals for signs and symptoms of hypersensitivity reactions following vaccination with ERVEBO. Appropriate medical treatment and supervision must be available in case of an anaphylactic event following the administration of ERVEBO.

5.2 Limitations of Vaccine Effectiveness

Vaccination with ERVEBO may not protect all individuals. Vaccinated individuals should continue to adhere to infection control practices to prevent *Zaire ebolavirus* infection and transmission.

5.3 Immunocompromised Individuals

The safety and effectiveness of ERVEBO have not been assessed in immunocompromised individuals. The effectiveness of ERVEBO in immunocompromised individuals may be diminished. The risk of vaccination with ERVEBO, a live virus vaccine, in immunocompromised individuals should be weighed against the risk of disease due to *Zaire ebolavirus*.

5.4 Transmission

Vaccine virus RNA has been detected by RT-PCR in blood, saliva, urine, and fluid from skin vesicles of vaccinated individuals. Transmission of vaccine virus is a theoretical possibility [see *Pharmacokinetics (12.3)*].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

The clinical development program for ERVEBO included clinical studies conducted in North America, Europe and Africa, in which 609 participants 12 months through 17 years of age and 18,007 participants 18 years of age and older received at least one dose of ERVEBO. The number of participants vaccinated with ERVEBO in double-blind, placebo-controlled trials was 2,913 and in open-label trials was 15,703.

In Study 1 (NCT02344407), conducted in Liberia (N=1,000), participants 18 years of age and older were randomized 1:1 to receive ERVEBO or saline placebo. Participants were assessed at Week 1 and Month 1 postvaccination for solicited local and systemic reactions. In a subset of participants (n=201), joint symptoms and signs were also solicited during a Week 2 visit. Memory aids were not used and postvaccination temperatures were measured only at study visits. Unsolicited adverse events were collected through Month 1 postvaccination. The median age of participants was 29 years, 63.6% were male and 100% were Black. Serious adverse events were monitored through 1-year postvaccination.

In Study 2 (NCT02503202), conducted in the United States, Canada and Spain (N=1,197), participants 18 through 65 years of age were randomized to receive ERVEBO (n=1,061) or saline placebo (n=133). Participants used a memory aid to record solicited local reactions from Days 1 to 5 postvaccination, and daily temperature measurements and solicited joint and skin events from Days 1 to 42 postvaccination. Unsolicited adverse reactions were collected through Day 42 postvaccination. The median age of participants was 42 years; 46.8% were male; 67.9% were White, 29.2% were Black or African American, 1.4% were Multi-racial, 0.8% were Asian, 0.4% were American Indian or Alaska Native, and 0.3% were Native Hawaiian or Pacific Islander; 14.5% were Hispanic or Latino. Serious adverse events were monitored through 6 months postvaccination, and a subset of participants (n=511) were monitored through 24 months postvaccination.

In Study 3 (Pan African Clinical Trials Registry, PACTR201503001057193), an open-label cluster-randomized study conducted in the Republic of Guinea, 5,643 participants 18 years of age and older received a dose of ERVEBO. The median age of vaccinated participants was 37 years, 68% were male and 100% were Black. Serious adverse events were monitored through 84 days postvaccination.

In Study 4 (NCT02378753), a randomized open-label study conducted in Sierra Leone, 7,998 participants 18 years of age and older received a dose of ERVEBO. The median age of participants was 31 years, 63% were male; 99.8% were Black and 0.2% collectively were Multi-racial, Asian or White. Serious adverse events were monitored through 180 days postvaccination.

In Study 5 (Pan African Clinical Trials Registry, PACTR201503001057193), an open-label safety and immunogenicity trial conducted in vaccinated frontline workers in the Republic of Guinea, implemented as Part B of Study 3, 2,016 participants 18 years of age and older received a dose of ERVEBO. The median age of vaccinated participants was 30 years, 75% were male and 100% were Black. Serious adverse events were monitored through 85 days postvaccination.

Study 6 (NCT02876328) is an ongoing, double-blind, randomized placebo-controlled study conducted in Liberia, Sierra Leone, Mali and the Republic of Guinea in which participants received ERVEBO or an investigational Ebola vaccine or placebo. A total of 155 participants 12 months through 2 years of age, 515 participants 3 through 11 years of age, 328 participants 12 through 17 years of age and 1,004 participants 18 years of age and older received a single dose of ERVEBO and saline placebo administered 56 days apart, or two doses of ERVEBO administered 56 days apart (not an approved dosing regimen), or two doses of saline placebo. Memory aids were not used. Participants were observed at the study site for 30 minutes after vaccination. Participants were assessed for solicited local and systemic reactions at study visits on day of vaccination (Day 0), Day 7, Day 14 and Day 28 after each vaccination. Postvaccination temperatures were obtained from participants 12 months through 17 years of age at daily contacts on Days 1 through 7, and on Day 14 and Day 28 after the first vaccination and Days 1 through 7 after the second vaccination. Postvaccination temperatures were obtained from participants 18 years of age and older at study visits. At each study visit, participants or their caregivers were queried about the occurrence of unsolicited adverse events. In this study, Grade 3 events were defined as symptoms causing inability to perform usual social and functional activities. Grade 4 events were defined as symptoms causing inability to perform basic self-care functions or medical or operative intervention indicated to prevent

permanent impairment, persistent disability, or death. The median age of participants 18 years of age and older was 27 years and 54.6% were male, and the median age of participants 12 months through 17 years of age was 8 years and 54.7% were male. Serious adverse events were monitored through 12 months postvaccination.

Eight additional studies (NCT02269423, NCT02280408, NCT02374385, NCT02314923, NCT02287480, NCT02283099, NCT02296983) contributed to the assessment of serious adverse reactions.

Adverse Reactions in Participants 18 Years of Age and Older

Table 1 presents the proportion of participants reporting solicited adverse reactions in Study 1.

Table 1: Percentage of Participants 18 Years of Age and Older with Solicited Local and Systemic Adverse Reactions After Vaccination (Study 1)

	<u>ERVEBO</u> %	<u>PLACEBO</u> %
<u>Injection-site reactions*</u>	<u>N=500</u>	<u>N=500</u>
Injection site pain	34.0	11.2
Local reactions (redness/swelling)	1.8	0.8
<u>Systemic adverse reactions†</u>	<u>N=498</u>	<u>N=499</u>
Headache	36.9	23.2
Feverishness	34.3	14.8
Muscle pain	32.5	22.8
Fatigue	18.5	13.4
Nausea	8.0	4.4
Joint pain/tenderness‡	7.0	5.8
Rash	3.6	3.2
Abnormal sweating	3.2	2.6
Arthropathy (joint redness/warmth)‡	0.6	0.2
Joint swelling‡	0.4	0.4
Joint stiffness‡	0.4	0.2

* Adverse reactions were solicited at 30 minutes, Week 1 and Month 1 postvaccination.

† Adverse reactions were solicited at Week 1 and Month 1 postvaccination.

‡ In a subset of participants (n=201), joint symptoms and signs were also solicited during a Week 2 visit.

In Study 1, 56.4% of participants reported at least one of the solicited systemic adverse reactions listed in Table 1 within seven days after vaccination. With the exception of one participant who reported events of moderate intensity (causing greater than minimal interference with daily activity), all others reported events of mild intensity (causing no or minimal interference with daily activity).

Table 2 presents the proportion of participants 18 years of age and older reporting solicited adverse reactions in Study 2.

Table 2: Percentage of Participants 18 Years of Age and Older with Solicited Local and Systemic Adverse Reactions After Vaccination (Study 2)

	<u>ERVEBO</u> %	<u>PLACEBO</u> %
<u>Injection-site reactions*</u>	<u>N=1051</u>	<u>N=133</u>
Injection-site pain	69.5	12.8
Injection-site swelling	16.5	3.0
Injection-site redness	11.9	1.5
<u>Systemic adverse reactions†</u>	<u>N=1051</u>	<u>N=133</u>
Joint pain	17.9	3.0
Arthritis (composite term)‡	4.7	0.0
Rash (composite term)§	3.8	1.5
Vesicular lesions¶	1.5	0.0

* Adverse reactions were solicited Days 1 to 5 postvaccination.

† Adverse reactions were solicited Day 1 through Day 42 postvaccination.

‡ Arthritis is a composite term that includes preferred terms of arthritis, monoarthritis, polyarthritis, osteoarthritis, joint swelling, or joint effusion.

§ Rash is a composite term that includes petechiae, purpura, rash, rash generalized, rash macular, rash papular and rash vesicular.

¶ Vesicular lesions include events reported as rash vesicular in the rash composite term and reported as blister.

In Study 2, 29 participants (2.8%) reported injection-site pain of severe intensity. Severe arthritis (arthritis and joint swelling) was reported by 8 participants (0.8%) and severe arthralgia was reported by 14 participants (1.3%). In this study, severe events were defined as incapacitating with inability to work or do usual activity.

Table 3 presents the proportion of participants 18 years of age and older reporting solicited adverse reactions in Study 6 within 28 days following administration of the first dose.

Table 3: Percentage of Participants 18 Years of Age and Older with Solicited Local and Systemic Adverse Reactions within 28 Days After the First Dose (Study 6)

	<u>ERVEBO</u>	<u>PLACEBO</u>
	<u>%</u>	<u>%</u>
<u>Injection-site reactions*</u>	<u>N=592</u>	<u>N=412</u>
Injection-site pain	21.5	4.1
Injection-site swelling	3.7	2.9
Injection-site erythema	1.4	2.4
<u>Systemic adverse reactions*</u>	<u>N=592</u>	<u>N=412</u>
Headache	55.1	43.4
Feverishness [†]	39.2	22.8
Myalgia	29.6	15.8
Somnolence [‡]	25.5	13.6
Arthralgia	18.6	10.7
Chills	16.7	8.5
Decreased appetite	15.2	9.5
Abdominal pain	13.0	11.2
Nausea	9.5	6.3
Vomiting	4.4	1.2
Mouth ulceration	2.2	0.5
Abnormal sweating	1.4	1.0
Joint swelling	0.7	0.0

* Adverse reactions were solicited postvaccination on day of vaccination (Day 0), Day 7, Day 14 and Day 28.

[†] Feverishness was not defined by a specific temperature measurement.

[‡] Includes: somnolence, reduced activity and fatigue.

Most (>98%) reactions presented in Table 3 were mild to moderate in intensity.

Adverse Reactions in Participants 12 Months through 17 Years of Age

Table 4 presents the proportion of participants reporting solicited adverse reactions within 28 days following administration of the first dose in Study 6.

Table 4: Percentage of Participants 12 Months through 17 Years of Age with Solicited Local and Systemic Adverse Reactions within 28 Days After First Dose (Study 6)

	<u>12 Months through 2 Years of Age</u>		<u>3 Years through 11 Years of Age</u>		<u>12 Years through 17 Years of Age</u>	
	<u>ERVEBO % N=95</u>	<u>PLACEBO % N=60</u>	<u>ERVEBO % N=310</u>	<u>PLACEBO % N=205</u>	<u>ERVEBO % N=203</u>	<u>PLACEBO % N=123</u>
<u>Injection-site reactions*</u>						
Injection-site pain	26.3	8.3	39.4	8.8	52.2	17.1
Injection-site swelling	5.3	3.3	2.6	2.0	2.5	2.4
Injection-site erythema	1.1	3.3	0.3	0.5	0.5	0
Injection-site pruritus	N/A	N/A	6.5	0	2.5	0.8
<u>Systemic adverse reactions*</u>						
Feverishness [†]	83.2	66.7	64.8	37.1	48.3	27.6
Crying	30.5	6.7	3.2	2.4	N/A	N/A
Decreased appetite	27.4	15.0	23.9	13.2	20.7	14.6
Somnolence [‡]	20.0	8.3	21.6	9.8	28.1	19.5
Diarrhea	18.9	16.7	2.9	4.4	3.9	4.1
Vomiting	16.8	10.0	11.0	8.8	3.9	3.3
Irritability	10.5	1.7	1.0	0.0	N/A	N/A
Screaming	9.5	1.7	0.6	0.5	N/A	N/A
Mouth ulceration	6.3	1.7	1.9	0.5	1.5	0
Chills	5.3	3.3	14.2	10.7	19.2	16.3
Headache	4.2	5.0	49.7	34.6	59.1	39.0
Abdominal pain	2.1	3.3	21.0	14.1	15.8	13.0
Abnormal sweating	2.1	3.3	1.3	2.0	4.9	0.8
Arthralgia	N/A	N/A	3.2	2.0	15.8	8.1
Dizziness	N/A	N/A	8.4	4.4	16.7	11.4
Myalgia	N/A	N/A	11.6	3.9	29.6	9.8
Nausea	0	1.7	8.4	3.4	8.4	8.1

* Adverse reactions were solicited postvaccination on day of vaccination (Day 0), Day 1 through Day 7, Day 14 and Day 28.

[†] Feverishness was not defined by a specific temperature measurement.

[‡] Includes: somnolence, reduced activity and fatigue.

N/A: Not applicable because not assessed in this age group.

Most (>98%) reactions presented in Table 4 were mild to moderate in intensity.

Table 5 presents the proportion of participants 12 months through 17 years of age reporting fever within 7 days following administration of the first dose in Study 6.

Table 5: Percentage of Participants 12 Months through 17 Years of Age with Fever Within 7 Days After the First Dose (Study 6)*

<u>Age</u>	<u>Maximum Temperature (Temporal)</u>	<u>ERVEBO %</u>	<u>PLACEBO %</u>
12 Months through 2 Years of Age	≥38.0°C to ≤38.4°C	<u>N=95</u> 3.2	<u>N=60</u> 1.7
	>38.4°C to ≤38.9°C	3.2	1.7
	>38.9°C to ≤40.0°C	0.0	1.7
	>40.0°C	0.0	0.0
3 Years through 11 Years of Age	≥38.0°C to ≤38.4°C	<u>N=310</u> 4.2	<u>N=205</u> 0.5
	>38.4°C to ≤38.9°C	1.0	1.5
	>38.9°C to ≤40.0°C	1.3	0.0
	>40.0°C	0.0	0.0
12 Years through 17 Years of Age	≥38.0°C to ≤38.4°C	<u>N=203</u> 2.5	<u>N=122</u> 0.8
	>38.4°C to ≤38.9°C	2.5	0.8
	>38.9°C to ≤40.0°C	2.5	0.8
	>40.0°C	0.0	0.0

* The use of antipyretic medication within 48 hours postvaccination was reported in 67% and 43% of participants 12 months through 2 years of age, 58% and 37% of participants 3 through 11 years of age, and 52% and 27% of participants 12 through 17 years of age for ERVEBO and placebo, respectively.

Unsolicited Adverse Reactions

In Study 2, the unsolicited adverse reaction of chills was reported in 7.3% of ERVEBO recipients compared to 0% of placebo recipients. Paresthesia was reported by 1.4% of ERVEBO recipients compared to 0% of those who received placebo in this study.

Arthralgia and Arthritis

In an analysis across blinded, placebo-controlled studies (excluding Study 6), arthralgia was reported to occur in 7% to 40% of vaccine recipients. Arthralgia was generally reported in the first few days following vaccination, was of mild to moderate intensity, and resolved within one week after onset. Severe arthralgia, defined as preventing daily activity, was reported in up to 3% of participants.

In an analysis across blinded, placebo-controlled studies (excluding Study 6) in which participants received ERVEBO or a lower dose formulation, arthritis (including events of arthritis, joint effusion, joint swelling, osteoarthritis, monoarthritis or polyarthritis) was reported to occur in 0% to 24% of participants, with all but one study reporting arthritis in <5% of participants. Most occurrences of arthritis were reported within the first few weeks following vaccination, were of mild to moderate intensity, and resolved within several weeks after onset. In one study conducted in Switzerland (NCT02287480), 102 participants received ERVEBO or a lower dose formulation. In this study, arthritis was reported to occur in 24% of participants and severe arthritis, defined as preventing daily activity, in 12% of participants. Joint effusion samples were obtained from three participants and all three tested positive for vaccine virus RNA by RT-PCR. Of all 24 participants with arthritis in this study, six participants reported recurrent or prolonged joint symptoms lasting up to 2 years following vaccination, the longest follow-up period.

Rash

In an analysis across blinded, placebo-controlled studies (excluding Study 6), rash was reported to occur after administration of ERVEBO, with all but one study reporting rash in <9% of participants. In one study (NCT02287480), rash was reported to occur in 25% (n=4) of ERVEBO recipients and 7.7% (n=1) of placebo recipients. In this study, cutaneous vasculitis was reported in two participants who received a lower dose formulation, neither of whom had evidence of systemic vasculitis. Vesicular fluid and skin biopsy samples taken from some participants reporting rash have tested positive for vaccine virus RNA by RT-PCR.

Decreases in Lymphocytes and Neutrophils

White blood cell counts were assessed in 697 participants who received ERVEBO. Decreases in lymphocytes were reported in up to 85% of participants and decreases in neutrophils were reported in up to 43% of participants. No associated infections were reported.

Serious Adverse Reactions

In 18,616 ERVEBO recipients, two serious adverse reactions of pyrexia were reported as vaccine-related. In addition, two serious adverse reactions of anaphylaxis were reported as vaccine-related. These serious adverse reactions occurred in participants 18 years of age and older, and none were fatal.

7 DRUG INTERACTIONS

7.1 Interference with Laboratory Tests

Following vaccination with ERVEBO, individuals may test positive for anti-Ebola glycoprotein (GP) antibody and/or Ebola GP nucleic acid or antigens. GP-based testing may have limited diagnostic value during the period of vaccine viremia, in the presence of vaccine-derived Ebola GP, and following antibody response to the vaccine [see *Pharmacokinetics (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

There are no adequate and well-controlled studies of ERVEBO in pregnant women, and human data available from clinical trials with ERVEBO are insufficient to establish the presence or absence of vaccine-associated risk during pregnancy.

The decision to vaccinate a woman who is pregnant should consider the woman's risk of exposure to *Zaire ebolavirus*.

A developmental toxicity study has been performed in female rats administered a single human dose of ERVEBO on four occasions; twice prior to mating, once during gestation and once during lactation. This study revealed no evidence of harm to the fetus due to ERVEBO [see *Animal Data below*].

Clinical Considerations

Disease-associated Maternal and/or Embryo/Fetal Risk

Fetal and neonatal outcomes are universally poor among pregnant women infected with *Zaire ebolavirus*. The majority of such pregnancies end in miscarriage or stillbirth. In pregnancies where live birth does occur, neonates generally do not survive.

Fetal/Neonatal Adverse Reactions

The potential for transmission of the vaccine virus from mother to the fetus/neonate is unknown.

Data

Animal Data

In a developmental toxicity study, female rats received a single human dose of ERVEBO by intramuscular injection on four occasions: 28 days and 7 days prior to mating, gestation day 6 and lactation day 7. No adverse effects on pre-weaning development up to post-natal day 21 were observed. There were no vaccine-related fetal malformations or variations observed.

8.2 Lactation

Risk Summary

Human data are not available to assess the impact of ERVEBO on milk production, its presence in breast milk, or its effects on the breastfed child. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ERVEBO and any potential adverse effects on the breastfed child from ERVEBO or from the underlying maternal condition. For preventive vaccines, the underlying condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

The safety and effectiveness of ERVEBO in individuals 12 months through 17 years of age have been established [see *Adverse Reactions (6.1) and Clinical Studies (14.2)*]. The safety and effectiveness of ERVEBO in individuals younger than 12 months of age have not been established.

8.5 Geriatric Use

Across the clinical development program, the total number of participants ≥ 65 years of age who received at least one dose of ERVEBO was 554.

Clinical studies of ERVEBO did not include sufficient numbers of participants 65 years of age and older to determine whether they respond differently from younger participants.

11 DESCRIPTION

ERVEBO (Ebola Zaire Vaccine, Live) is a sterile suspension for intramuscular injection. ERVEBO is a live recombinant viral vaccine consisting of a vesicular stomatitis virus (VSV) backbone deleted for the VSV envelope glycoprotein and substituted with the envelope glycoprotein of the *Zaire ebolavirus* (Kikwit 1995 strain). The vaccine virus is grown in serum-free Vero cell cultures. The virus is harvested from the cell culture medium, purified, formulated with stabilizer solution, filled into vials and stored frozen. When thawed, ERVEBO is a colorless to slightly brownish-yellow liquid with no particulates visible.

Each 1 mL dose of ERVEBO contains a minimum of 72 million plaque forming units (pfu) of vaccine virus in a stabilizer solution containing 10 mM Tromethamine (Tris) and 2.5 mg/mL rice-derived recombinant human serum albumin. Each 1 mL dose may contain residual amounts of host cell DNA (≤ 10 ng) and benzonase (≤ 15 ng). The vaccine may contain trace amounts of rice protein. The product contains no preservatives.

The vaccine vial stopper is not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Immunization with ERVEBO results in an immune response and protection from disease caused by *Zaire ebolavirus*. The relative contributions of innate, humoral and cell-mediated immunity to protection from *Zaire ebolavirus* are unknown.

12.3 Pharmacokinetics

Viremia

Vaccine viremia was evaluated in 186 participants enrolled in seven clinical studies who were vaccinated with ERVEBO. Vaccine virus RNA was detected by RT-PCR in the plasma of most participants from Day 1 to Day 7 postvaccination with one participant having a positive plasma RT-PCR result 14 days after vaccination.

Shedding

Shedding of vaccine virus into the urine or saliva was evaluated in 359 participants enrolled in 8 clinical studies who were vaccinated with ERVEBO or lower dose formulations. Vaccine virus RNA was detected by RT-PCR in the urine or saliva of some participants at timepoints ranging from Day 1 through Day 14 postvaccination. In the 3 studies that assessed shedding at Day 28, no samples tested positive. In Study 6, 31.7% (19/60) of participants 12 months through 17 years of age enrolled in a substudy shed vaccine virus in saliva following vaccination. Viral shedding was greatest on Day 7 and declined thereafter, with no shedding detected after Day 28.

Vaccine virus RNA was detected by RT-PCR in vesicular fluid samples from some participants. In one participant, a sample collected 20 days after vaccination tested positive for vaccine virus RNA by RT-PCR.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ERVEBO has not been evaluated for the potential to cause carcinogenicity, genotoxicity or impairment of male fertility. ERVEBO administered to female rats had no effects on fertility [see *Use in Specific Populations (8.1)*].

14 CLINICAL STUDIES

14.1 Clinical Efficacy

Clinical efficacy of ERVEBO was assessed in Study 3.

Study 3 (Ring vaccination study) was an open-label, randomized cluster (ring) vaccination study conducted in the Republic of Guinea during the 2014 outbreak. Each cluster was composed of contacts and contacts of contacts of individuals with laboratory-confirmed Ebola virus disease (EVD). Clusters were randomized to receive either an "immediate" vaccination or a 21-day "delayed" vaccination. In the primary

efficacy analysis, 3,537 participants ≥18 years of age were considered contacts and contacts of contacts of an index case with laboratory-confirmed EVD. Of these, 2,108 were included in 51 immediate vaccination clusters, and 1,429 were included in 46 delayed vaccination clusters.

The median age of participants in the primary efficacy analysis was 40 years. The majority were male, comprising 70.4% and 70.3% in the randomized immediate and delayed clusters, respectively.

In the primary efficacy analysis, the number of cases of laboratory-confirmed EVD in participants vaccinated in immediate vaccination clusters was compared to the number of cases in participants in delayed vaccination clusters. Cases of EVD that occurred between Day 10 and Day 31 post-randomization of the cluster were included in the analysis. Vaccine efficacy was 100% (95% CI: 63.5% to 100%); no cases of confirmed EVD were observed in the immediate vaccination clusters, and 10 confirmed cases of EVD were observed in a total of 4 delayed vaccination clusters between Day 10 and Day 31 post-randomization.

14.2 Clinical Immunogenicity

A measure of the immune response that confers protection against EVD is unknown.

Clinical Immunogenicity in Individuals 18 Years of Age and Older Across Geographic Areas

Four studies assessed antibody responses to ERVEBO in participants 18 years of age and older (Study 1, Study 2, Study 4 and Study 5), including 477 participants in Liberia, 506 participants in Sierra Leone, 915 participants in the US, Canada, and Spain (n=865 US participants) and 1,217 participants in the Republic of Guinea. *Zaire ebolavirus* (Kikwit) GP-specific immunoglobulin G (IgG) was detected by enzyme linked immunosorbent assay (GP-ELISA). Vaccine virus neutralizing antibody was detected by a plaque reduction neutralization test (PRNT).

Antibody responses among participants in the study conducted in the US, Canada, and Spain (Study 2) were similar to those among participants in the studies conducted in Liberia (Study 1), Sierra Leone (Study 4) and the Republic of Guinea (Study 5).

Clinical Immunogenicity in Individuals 12 Months through 17 Years of Age

A fifth study (Study 6) conducted in Liberia, Sierra Leone, Mali and the Republic of Guinea assessed antibody geometric mean titers (GMT) to ERVEBO in 386 participants 12 months through 17 years of age compared to 386 participants 18 years of age and older. *Zaire ebolavirus* (Kikwit) GP-specific immunoglobulin G (IgG) was detected by enzyme linked immunosorbent assay (GP-ELISA). GMTs at Day 28 after vaccination with ERVEBO in participants 12 months through 17 years of age were non-inferior to those in participants 18 years of age and older (see Table 6).

Table 6: Non-inferiority Analysis of Pooled Geometric Mean Titers at Day 28 for the GP-ELISA (Study 6)

<u>Individuals 12 Months through 17 Years of Age</u> n=499	<u>Individuals 18 Years of Age and Older</u> n=519	<u>GMT ratio* (95% CI)</u>
<u>GMT (95% CI)</u> 1748.8 (1585.6, 1928.7)	<u>GMT (95% CI)</u> 1234.4 (1132.5, 1345.4)	1.42 (1.24, 1.62)

The Per-Protocol Immunogenicity Population was the primary population for the immunogenicity analyses in Study 6 and includes all vaccinated participants with serology data who were compliant with the protocol and had a serum sample collected within an acceptable day range.

n=Number of participants contributing to the analysis.

CI=Confidence interval; GMT=geometric mean titer; GP-ELISA=glycoprotein enzyme-linked immunosorbent assay.

Study 6 used gamma irradiation of specimens to reduce risk of wild-type Ebola virus infection of laboratory workers.

* GMT (individuals 12 months through 17 years of age) / GMT (individuals 18 years of age and older); Non-inferiority is declared if the lower bound of the 2-sided 95% CI for the GMT ratio is greater than 0.5.

16 HOW SUPPLIED/STORAGE AND HANDLING

Carton of ten 1 mL single-dose vials. NDC 0006-4293-02

Store frozen at -80°C to -60°C (-112°F to -76°F). Store in the original carton to protect from light.

Do not thaw the vial in a refrigerator. Thaw the vial at room temperature until no visible ice is present.

Use the vaccine immediately after thawing. If not used immediately, a thawed vial can be stored refrigerated at 2°C to 8°C (35.6°F to 46.4°F) for a total time of no more than 2 weeks and at room temperature (up to 25°C; 77°F) for a total time of no more than 4 hours. Protect from light. Do not re-freeze thawed vaccine.

17 PATIENT COUNSELING INFORMATION

Advise the vaccine recipients, parents or guardians to read the FDA-approved patient labeling (Patient Information).

Advise vaccine recipients, parents or guardians of the following:

- ERVEBO has not been demonstrated to provide protection against disease caused by viruses other than *Zaire ebolavirus*. After vaccination with ERVEBO, individuals at risk should continue to protect themselves from exposure to *Zaire ebolavirus*.
- ERVEBO may not protect all vaccinated individuals.
- Transmission of vaccine virus is a theoretical possibility. Vaccine virus RNA has been detected in blood, saliva, or urine for up to 14 days after vaccination. The duration of shedding is not known; however, samples taken 28 days after vaccination tested negative. Vaccine virus RNA has been detected in fluid from skin vesicles that appeared after vaccination.

Instruct vaccine recipients, parents or guardians to:

- Report any adverse reactions to their health care provider.
- Seek immediate medical attention if any signs or symptoms of a hypersensitivity reaction occur after vaccination [see *Contraindications (4)*].

Manufactured by: Merck Sharp & Dohme LLC
Rahway, NJ 07065, USA

For patent information: www.msd.com/research/patent

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