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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use IXCHIQ safely and effectively. See full prescribing information for IXCHIQ.

IXCHIQ (Chikungunya Vaccine, Live) Solution for Intramuscular Injection
Initial U.S. Approval: 2023

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

Indications and Usage, Limitations of Use (1)	8/2025
Warnings and Precautions, Risk of Serious, Severe or Prolonged Chikungunya-like Illness (5.2)	8/2025

----------INDICATIONS AND USAGE----------
IXCHIQ is a vaccine indicated for the prevention of disease caused by chikungunya virus (CHIKV) in individuals 18 years of age and older who are at high risk of exposure to CHIKV. (1)
This indication is approved under accelerated approval based on anti-CHIKV neutralizing antibody titers. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory studies.

Limitations of use:
Vaccination with IXCHIQ is not advisable for most U.S. travelers. For most U.S. travelers, the risk of exposure to CHIKV is low.
The Centers for Disease Control and Prevention provides resources for assessing likelihood of exposure to CHIKV among travelers and laboratory workers (Chikungunya Vaccine Information for Healthcare Providers).

The decision to administer IXCHIQ should take into consideration an individual's risk of severe or chronic disease outcomes if infected with CHIKV and risks of serious, severe, or prolonged chikungunya-like illness caused by vaccination with IXCHIQ (5.2, 6.1, 6.2), in addition to the risk of exposure to CHIKV. For travelers, factors to consider include level of disease activity at destination, duration of travel or residence, and likelihood of exposure to mosquitoes.

----------DOSAGE AND ADMINISTRATION----------
For intramuscular use only.
Administer IXCHIQ as a single approximately 0.5 mL dose. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
IXCHIQ is a solution for injection. After reconstitution, a single dose is approximately 0.5 mL. (3)

----------CONTRAINDICATIONS----------
- Immunocompromised individuals. (4.1)
- Individuals with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of IXCHIQ. (4.2)

----------WARNINGS AND PRECAUTIONS----------
- IXCHIQ may cause serious, severe, or prolonged chikungunya-like illness. Serious, severe, or prolonged chikungunya-like illness has been reported in clinical trials. Serious chikungunya-like illness, resulting in hospitalization, including a case of encephalitis with fatal outcome, has been reported during postmarketing use with IXCHIQ. Limited available postmarketing data suggest that individuals 65 years of age and older with one or more chronic medical conditions may have an increased risk for serious chikungunya-like illness following vaccination with IXCHIQ. (5.2, 6.1, 6.2)
- Vertical transmission of wild-type CHIKV from pregnant individuals with viremia at delivery is common and can cause potentially fatal CHIKV disease in neonates. Vaccine viremia occurs in the first week following administration of IXCHIQ, with resolution of viremia by 14 days after vaccination. It is not known if the vaccine virus can be vertically transmitted and cause fetal or neonatal adverse reactions. (5.3)
- Syncope (fainting) may occur in association with administration of injectable vaccines, including IXCHIQ. Procedures should be in place to avoid injury from fainting. (5.4)

----------ADVERSE REACTIONS----------
In clinical studies, the most common solicited injection site reaction (>10%) was tenderness (10.6%). The most common solicited systemic adverse reactions (>10%) were headache (31.6%), fatigue (28.5%), myalgia (23.9%), arthralgia (17.2%), fever (13.5%) and nausea (11.2%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Valneva USA Inc. at 1-844-349-4276 or VAERS at 1-800-822-7967 or http://vaers.hhs.gov.

---------- USE IN SPECIFIC POPULATIONS ----------
A decision to administer IXCHIQ during pregnancy should take into consideration the individual's risk of wild-type CHIKV infection, gestational age, and risks to the fetus or neonate from vertical transmission of wild-type CHIKV. (8.1)

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

Revised: 8/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IXCHIQ is a vaccine indicated for the prevention of disease caused by chikungunya virus (CHIKV) in individuals 18 years of age and older who are at high risk of exposure to CHIKV.
This indication is approved under accelerated approval based on anti-CHIKV neutralizing antibody levels [*see Clinical Studies (14)*]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory studies.

Limitations of use:

Vaccination with IXCHIQ is not advisable for most U.S. travelers. For most U.S. travelers, the risk of exposure to CHIKV is low. The Centers for Disease Control and Prevention provides resources for assessing likelihood of exposure to CHIKV among travelers and laboratory workers (Chikungunya Vaccine Information for Healthcare Providers).

The decision to administer IXCHIQ should take into consideration an individual's risk of severe or chronic disease outcomes if infected with CHIKV and risks of serious, severe, or prolonged chikungunya-like illness caused by vaccination with IXCHIQ *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1 and 6.2)]*, in addition to the risk of exposure to CHIKV. For travelers, factors to consider include level of disease activity at destination, duration of travel or residence, and likelihood of exposure to mosquitoes.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Dose and Schedule

After reconstitution, a single dose of IXCHIQ is approximately 0.5 mL.

Administer a single dose of IXCHIQ by intramuscular injection.

2.2 Preparation for Administration

Reconstitute the Lyophilized Antigen Component, Live (a white to slightly yellowish powder) only with the accompanying Sterile Water Diluent Component to form IXCHIQ. The reconstituted vaccine is a clear, colorless to slightly yellowish liquid solution. 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 exists, do not administer the vaccine.

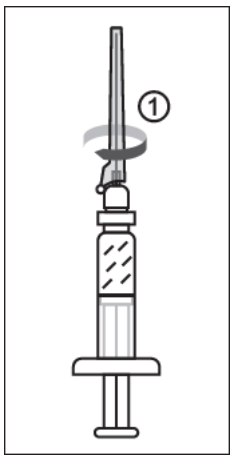

Figure 1

1) Remove the cap from the syringe of Sterile Water Diluent Component. Attach a needle to the Luer lock of the syringe

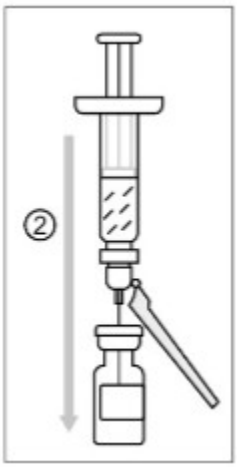

Figure 2

2) Cleanse the stopper of the vial of Lyophilized Antigen Component, Live. Slowly transfer the entire contents of the prefilled syringe of Sterile Water Diluent Component into the vial.

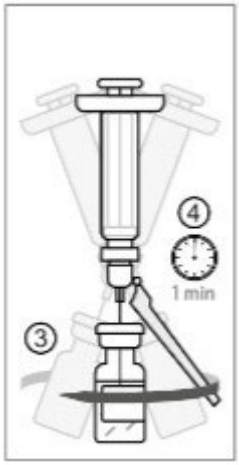

Figure 3

3) Gently swirl the vial to dissolve the Lyophilized Antigen Component, Live. Do not shake or invert the vial.

4) After swirling, wait for at least one minute for complete reconstitution of the vaccine.

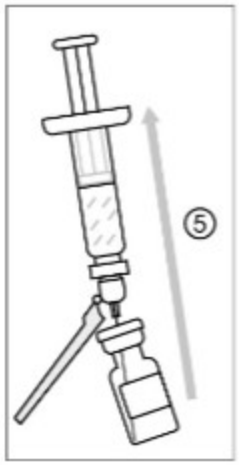

Figure 4

5) After reconstitution, slightly tilt the vial and withdraw the entire contents into the syringe. Do not invert the vial.

2.3 Administration

After reconstitution, immediately administer IXCHIQ intramuscularly.

3 DOSAGE FORMS AND STRENGTHS

IXCHIQ is a solution for injection. After reconstitution, a single dose is approximately 0.5 mL.

4 CONTRAINDICATIONS

4.1 Immunocompromised Individuals

Do not administer IXCHIQ to individuals who are immunodeficient or immunosuppressed due to disease, condition, or medical therapy (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy or patients with HIV infection who are severely immunocompromised).

4.2 Severe Allergic Reactions

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

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of IXCHIQ.

5.2 Risk of Serious, Severe or Prolonged Chikungunya-like Illness

Vaccination with IXCHIQ may cause serious, severe or prolonged chikungunya-like illness *[see Adverse Reactions (6.1)]* with clinical manifestations that are consistent with disease caused by wild-type chikungunya virus and with onset typically within the first two weeks following vaccination.

In a clinical trial, severe chikungunya-like illness that prevented daily activity and/or required medical intervention occurred in 1.6% of 3,082 IXCHIQ recipients and no placebo recipients. Two IXCHIQ recipients required hospitalization for severe myalgia and for hypovolemic hyponatremia and atrial fibrillation, respectively. Fourteen IXCHIQ recipients had prolonged (duration at least 30 days) chikungunya-like illness *[see Adverse Reactions (6.1)]*.

During postmarketing use with IXCHIQ, serious chikungunya-like illness resulting in hospitalization, including a case of encephalitis with fatal outcome, has been reported [*see Adverse Reactions (6.2)*]. Limited available

postmarketing data suggest that individuals 65 years of age and older with one or more chronic medical conditions may have an increased risk for serious chikungunya-like illness following vaccination with IXCHIQ.

5.3 Potential for Vertical Transmission of Vaccine Virus and Fetal/Neonatal Adverse Reactions

Vertical transmission of wild-type CHIKV to neonates from pregnant individuals with viremia at delivery is common and can cause severe, potentially fatal CHIKV disease in neonates. Vertical transmission of wild-type CHIKV and fetal death attributable to CHIKV in the context of antepartum infection has been reported to occur infrequently *[see Use in Specific Populations (8.1)]*.

Vaccine viremia occurs in the first week following administration of IXCHIQ, with resolution of viremia by 14 days after vaccination *[see Clinical Pharmacology (12.2)]*. It is not known if the vaccine virus can be transmitted from a pregnant individual to the fetus or neonate and cause fetal or neonatal adverse reactions.

Decisions to administer IXCHIQ during pregnancy should take into consideration the individual's risk of exposure to wild-type CHIKV, gestational age, and risks to the fetus or neonate from vertical transmission of wild-type CHIKV.

Closely monitor neonates for 7 days after birth for potential disease due to vaccine virus if they are born within 14 days of their mother receiving IXCHIQ.

5.4 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines including IXCHIQ. Procedures should be in place to avoid injury from fainting.

5.5 Limitation of Vaccine Effectiveness

Vaccination with IXCHIQ may not protect all individuals.

6 ADVERSE REACTIONS

In clinical studies, the most common solicited injection site reaction (>10%) was tenderness (10.6%). The most common solicited systemic adverse reactions (>10%) were headache (31.6%), fatigue (28.5%), myalgia (23.9%), arthralgia (17.2%), fever (13.5%) and nausea (11.2%).

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 safety of IXCHIQ was evaluated in two clinical studies [Study 1 (NCT04546724), Study 2 (NCT04786444)], both conducted in North America, in which a total of 3,490 participants 18 years of age and older received a dose of IXCHIQ.

Study 1 was a randomized, placebo-controlled, double-blinded study, in which participants were vaccinated with a single dose of IXCHIQ (n=3,082) or placebo (Phosphate Buffered Saline) (n=1,033). Study 2 was a non-placebo-controlled study where 408 participants were vaccinated with a single dose of IXCHIQ. Among the overall 4,523 participants enrolled in those studies, 54.7% were female; 80.1% were White, 14.0% Black or African American, 1.9% Asian, 0.8% American Indian or Alaska Native, 0.4% Native Hawaiian or Pacific Islander, 2.7% Other racial groups; and 17.2% were Hispanic or Latino.

In Studies 1 and 2, solicited adverse reactions, including injection site and systemic adverse reactions, were collected via electronic diary in the first 10 days post-vaccination. An electronic memory aid was distributed to each participant for the collection of safety information outside the first ten post-vaccination days until the next visit. Unsolicited adverse events, chikungunya-like illness, and serious adverse events were monitored through 6 months post-vaccination. In Study 1, hematology parameters were assessed at enrollment, 7, 28, 84 and 180 days post-vaccination in a subset of participants who were evaluated for seroresponse to vaccination (immunogenicity subset). *[see Clinical Studies (14)]*.

Solicited Adverse Reactions

In Study 1, the median age of participants was 45 years (range 18 through 94 years); 54.7% were female and 45.3% male; 80.4% were White, 13.9% Black or African American, 1.7% Asian, 0.8% American Indian or Alaska Native, 0.4% Native Hawaiian or Pacific Islander, 2.8% Other racial groups; and 17.5% were Hispanic or Latino. IXCHIQ and placebo groups were similar with regard to demographics.

The percentage of participants in Study 1 reporting solicited local and systemic adverse reactions is shown in Table 1. The median day of onset was Day 2 for local reactions (Day 1 was the day of vaccination) and Day 5 for systemic reactions. Local and systemic adverse reactions resolved with a median duration of 2 days.

Table 1. Percentage of Participants with Solicited Local and Systemic Adverse Reactions Within 10 Days After Vaccination (Study 1§)

Category	**IXCHIQ** (N=3,082) %	**Placebo** (N=1,033) %
Solicited Injection Site Adverse Reaction[a]		
Tenderness (any)[b]	10.6	8.1
Tenderness (severe)	0	0
Pain (any)[c]	6.2	3.7
Pain (severe)	0.03	0
Erythema/Redness (≥ 2.5 cm)[d]	1.5	1.5
Induration (≥ 2.5 cm)[d]	1.4	0.8
Swelling (≥ 2.5 cm)[d]	0.7	0.8
Solicited Systemic Adverse Reaction[a]		
Headache (any)[a]	31.6	14.7
Headache (severe)[e]	0.1	0.1
Fatigue (any)[a]	28.5	12.7
Fatigue (severe)[e]	0.2	0
Myalgia/Muscle Pain (any)[a]	23.9	7.4
Myalgia/Muscle Pain (severe)[e]	0.3	0
Arthralgia/Joint Pain (any)[a]	17.2	4.9
Arthralgia/Joint Pain (severe)[e]	0.3	0
Fever (any)[f]	13.5	0.9
Fever (severe or worse)[g]	1.4	0

Nausea (any)[a]	11.2	5.6
Nausea (severe)[c]	0	0.1
Rash (any)[a]	2.3	0.5
Rash (severe)[h]	0	0
Vomiting (any)[a]	1.9	1.0
Vomiting (severe)[e]	0	0.1

§NCT04546724
N=Number of participants
[a] Severity=mild, moderate, severe intensity.
[b] defined as mild (mild discomfort to touch), moderate (discomfort with movement), severe (significant discomfort at rest). Any potentially life threatening event (emergency room visit or hospitalization) was to be reported as severe.
[c] defined as mild (does not interfere with activity), moderate (repeated use of non-narcotic pain reliever > 24 hours or interferes with activity), severe (any use of narcotic pain reliever or prevents daily activity). Any potentially life threatening event (emergency room visit or hospitalization) was to be reported as severe.
[d] No participants had erythema, induration or swelling >10 cm
[e] Severe=Prevents daily activity (for fatigue, myalgia, and arthralgia); Prevents daily activity and requires medical intervention (for headache, nausea, vomiting)
[f] defined as temperature ≥38.0°C (100.4°F)
[g] defined as temperature ≥39.0°C (102.1°F)
[h] Severe=Macules/papules covering >30% body surface area with or without associated symptoms; limiting self-care activity of daily living.

Hematology Parameters

In Study 1, hematology parameters were assessed at 7, 28, 84 and 180 days post-vaccination in the immunogenicity subset. Percentages of study participants with abnormally low leukocyte, neutrophil and lymphocyte counts are presented by maximum grade post-vaccination in Table 2. Abnormal leukocyte, neutrophil and lymphocyte counts were more frequently observed in IXCHIQ recipients than placebo recipients. Of 186 participants with abnormal cell counts at the 7-day post-vaccination assessment, 171 (171/186, 92%) had available hematology results at the 28-day post-vaccination assessment, of which 150 (150/171, 88%) were in the normal range.

Table 2. Abnormal Hematology Results by Maximum Grade Post-vaccination (Study 1§)

Laboratory Parameter Grade	**IXCHIQ**[a] (N=372) n (%)	**Placebo**[a] (N=125) n (%)
Leukocytes		
Grade 1 2,500 – 3,500 cell/mm^3	99 (27.3)	7 (5.8)
Grade 2 1,500 – 2499, cell/mm^3	16 (4.4)	0
Grade 3 1,000 – 1,499 cell/mm^3	1 (0.3)	0
Grade 4 <1,000 cell/mm^3	0	0
Neutrophils		
Grade 1 1,500 – 2,000 cell/mm^3	100 (27.6)	14 (11.6)
Grade 2 1,000 – 1,499 cell/mm^3	41 (11.3)	1 (0.8)
Grade 3 500 – 999 cell/mm^3	11 (3.0)	0
Grade 4 < 500 cell/mm^3	1 (0.3)	0
Lymphocytes		
Grade 1 750 – 1,000 cell/mm^3	69 (19.1)	8 (6.6)
Grade 2 500 – 749 cell/mm^3	15 (4.1)	1 (0.8)
Grade 3 250 – 499 cell/mm^3	1 (0.3)	0
Grade 4 <250 cell/mm^3	0	0

§ NCT04546724, immunogenicity subset
[a] Individuals are included only once under the highest grade. Percentages are based on the number of individuals with at least one postbaseline result.

Unsolicited Adverse Events

Unsolicited adverse events that occurred within 28 days following vaccination were reported in 21.8% of 3,082 participants who received IXCHIQ versus 13.3% of 1,033 participants who received placebo. Chills was reported by 1.8% of IXCHIQ recipients and 0.2% of placebo recipients; diarrhea was reported by 1.4% of IXCHIQ recipients and 0.4% of placebo recipients; back pain was reported by 1.1% of IXCHIQ recipients and 0.6% of placebo recipients, lymphadenopathy was reported by 0.9% of IXCHIQ recipients and 0% of placebo recipients. Chills, diarrhea, back pain, and lymphadenopathy are likely related to vaccination. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of unsolicited adverse events that would suggest a causal relationship to IXCHIQ.

Serious Adverse Reactions

Among 3,490 IXCHIQ recipients, two (both from Study 1) reported serious adverse reactions. One IXCHIQ recipient reported myalgia and one reported atrial fibrillation and hypovolemic hyponatremia. These adverse reactions are further described under the subheading Chikungunya-Like Illness.

Chikungunya-Like Illness

In Study 1, participants were monitored for a cluster of symptoms consistent with disease caused by wild-type chikungunya virus. Chikungunya-like illness was defined as fever (≥38 °C / 100.4 °F) and one or more of any of the following: arthralgia or arthritis, myalgia, headache, back pain, rash, lymphadenopathy, or certain neurological, cardiac or ocular symptoms that occurred with an onset within 30 days after vaccination. Severe chikungunya-like illnesses were those that prevented daily activity and/or required medical intervention.

Among Study 1 participants, 361 (11.7%) in the IXCHIQ group (n= 3,082) reported chikungunya-like illness, including 48 participants (1.6%) who reported severe chikungunya-like illness. Six (0.6%) participants in the placebo group (n=1,033) reported chikungunya-like illness, none of which were severe. The frequencies of chikungunya-like symptoms among the IXCHIQ recipients with chikungunya-like illness are presented in Table 3.

Table 3. Frequency of Chikungunya-Like Symptoms Among Participants With Chikungunya-Like Illness (Study 1§)

Chikungunya-Like Symptom Chikungunya-Like Symptom (severe)	**IXCHIQ** (N=361) % (n)
Pyrexia (any) Pyrexia (severe)	100 (361) 10.8 (39)
Headache (any) Headache (severe)	77.6 (280) 0.3 (1)
Fatigue (any) Fatigue (severe)	73.1 (264) 0.6 (2)
Myalgia (any) Myalgia (severe)	59.6 (215) 0.8 (3)
Arthralgia (any) Arthralgia (severe)	44.0 (159) 1.4 (5)
Chills (any)[a]	8.0 (29)
Rash (any)[a]	6.1 (22)
Back pain (any) Back pain (severe)	3.6 (13) 0.3 (1)
Lymphadenopathy (any)[a]	2.5 (9)
Dizziness (any)[a]	1.7 (6)
Pain (any)[a]	1.1 (4)
Paresthesia (any)[a]	0.8 (3)

Hyperhidrosis (any)[a]	0.6 (2)
Edema peripheral (any)[a]	0.6 (2)
Asthenia (any)[a]	0.3 (1)
Ataxia (any)[a]	0.3 (1)
Atrial fibrillation (any) Atrial fibrillation (severe)	0.3 (1) 0.3 (1)
Feeling abnormal (any)[a]	0.3 (1)
Hypoesthesia (any)[a]	0.3 (1)
Influenza like illness (any)[a]	0.3 (1)
Neuropathy peripheral (any)[a]	0.3 (1)
Rash erythematous (any)[a]	0.3 (1)
Syncope (any)[a]	0.3 (1)

§NCT04546724
N=Number of participants with chikungunya-like illness; n=number of participants with chikungunya-like symptom.
[a] No severe chikungunya-like symptoms reported.

The median onset of chikungunya-like illness in IXCHIQ recipients was 4.0 days (range 1 to 11 days) after vaccination. The median duration of chikungunya-like illness in IXCHIQ recipients was 4.0 days (range 1 day to at least 6 months) after vaccination.

Fourteen IXCHIQ recipients had prolonged (duration at least 30 days) chikungunya-like illness (median duration 94 days, range 30 days to at least 6 months). Prolonged fatigue, headache, and myalgia were each reported by three participants. Prolonged arthralgia was reported by five participants, including a 46-year-old male who reported severe arthralgia and back pain that lasted for at least 51 days after vaccination and a 50-year-old female who reported polyarthralgia and nodular swelling of joints in fingers and foot that lasted for at least 6 months after vaccination.

Two IXCHIQ recipients experienced serious chikungunya-like illness. A 58-year-old female with a history of fibromyalgia experienced severe myalgia, mild arthralgia, tachycardia and tachypnea, with onset of symptoms 1 to 2 days after vaccination, was hospitalized on Days 4 through 10 post-vaccination, and fully recovered, with myalgia resolving after 30 days. A 66-year-old male experienced severe fever on Days 5 through 11 post-vaccination, was hospitalized on Days 10 through 12 post-vaccination and found to have atrial fibrillation, increased troponin, increased brain natriuretic peptide and hypovolemic hyponatremia, and fully recovered. This study participant was included in a subset of participants assessed for vaccine viremia 7 days after vaccination and was found to be viremic.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use with IXCHIQ. Because adverse events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Infections and Infestations: Chikungunya-like illness

Serious chikungunya-like illness

Adverse reactions in postmarketing reports which are consistent with serious chikungunya-like illness *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]* include arthralgia, asthenia, atrial flutter, back pain, encephalitis (fatal), encephalopathy, headache, meningismus/aseptic meningitis, myalgia, photophobia, tachycardia, thrombocytopenia, and troponin increased.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to IXCHIQ during pregnancy. Individuals who receive IXCHIQ during pregnancy are encouraged to contact directly, or have their healthcare professional contact, OXON Epidemiology at 1-855-417-6214 to enroll in or obtain information about the registry.

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US 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 IXCHIQ in pregnant individuals, and human data available from clinical trials with IXCHIQ are insufficient to establish the presence or absence of vaccine-associated risk during pregnancy.

A developmental study was conducted in female rats. Animals were administered a single human dose of IXCHIQ on 2 occasions, once prior to mating and once during gestation. This study revealed no evidence of harm to the fetus and no adverse effects on post-natal development due to the vaccine [*see Animal Data*].

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Vertical transmission of wild-type CHIKV to neonates from pregnant individuals with viremia at delivery is common and can cause severe, potentially fatal CHIKV disease in neonates, with neurologic (e.g., encephalopathy, intracranial hemorrhage) and myocardial manifestations. Vertical transmission of wild-type CHIKV and fetal death attributable to CHIKV in the context of antepartum infection has been reported to occur infrequently *[see Data]*.

Fetal/neonatal adverse reactions

Vaccine viremia occurred in the first week following administration of a vaccine containing the same attenuated CHIKV as in IXCHIQ *[see Description (11)],* with resolution of viremia by 14 days after vaccination [*see Clinical Pharmacology (12.2)]*. It is not known if the vaccine virus can be transmitted from a pregnant individual to the fetus or neonate and cause fetal or neonatal adverse reactions.

Decisions to administer IXCHIQ during pregnancy should take into consideration the individual's risk of exposure to wild-type CHIKV, gestational age, and risks to the fetus or neonate from vertical transmission of wild-type CHIKV.

Closely monitor neonates for 7 days after birth for potential disease due to vaccine virus if they are born within 14 days of their mother receiving IXCHIQ.

Data

Human data

In a prospective study conducted during an outbreak of CHIKV, vertical transmission of wild-type CHIKV to neonates from infected pregnant individuals was assessed. Among pregnant individuals infected prepartum (N=22) or intrapartum (N=39) (symptomatic between day -7 and day -3, or day -2 and day 2 around delivery, respectively and concomitant positive serum CHIKV RT-PCR or IgM serology when PCR not available) vertical transmission occurred in 19, all with an intrapartum infection (vertical transmission rate of 48.7% for intrapartum infections). Severe CHIKV disease was reported in 52.6% (10/19) of these infected neonates. Among 678 pregnant individuals infected antepartum (symptomatic between conception and the week preceding labor and positive serum CHIKV RT-PCR or IgM serology) fetal death attributed to CHIKV occurred in three (0.4%). In these three cases, onset of CHIKV symptoms in the pregnant individual ranged from approximately 12 weeks to 15 weeks gestation and the fetal death occurred approximately two weeks later. For these fetal deaths, amniotic fluid before fetal death was CHIKV RT-PCR positive. CHIKV RNA was detected in the placenta and in the fetal brain for two.[1]

Animal data

In a pre- and post-natal developmental study with an embryo-fetal development toxicity phase conducted in female rats, a full human dose of IXCHIQ (0.5 mL) was administered by intramuscular injection on 2 occasions to determine the effect on female fertility, reproductive performance, and pre- and post-natal development: 14 days prior to mating, and on gestation day 6. No vaccine related adverse effects on fetal development, reproductive performance, and pre- and post-natal development were reported.

8.2 Lactation

Risk Summary

Human data are not available to assess the impact of IXCHIQ 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 IXCHIQ and any potential adverse effects on the breastfed child from IXCHIQ or from the underlying maternal condition. For preventive vaccines, the underlying condition is susceptibility to disease prevented by the vaccine.

Clinical Considerations

Fetal/neonatal adverse reactions

Vaccine viremia occurs after vaccination. In a clinical trial, vaccine virus was not detectable at 14 days after vaccination *[See Clinical Pharmacology (12.2)]*. The potential for transmission of the vaccine virus from mother to infant through breastmilk is unknown.

8.4 Pediatric Use

The safety and effectiveness of IXCHIQ in individuals younger than 18 years of age have not been established.

8.5 Geriatric Use

Of the total number of participants in clinical studies of IXCHIQ 9.6% (n=346) were 65 years of age and older, while 1.6% (n=59) were 75 and older. *[See Adverse Reactions (6.1) and Clinical Studies (14)]*. In Study 1, no overall difference in effectiveness was observed between participants 65 years of age and older and younger participants. Study 1 did not include sufficient numbers of participants 65 years of age and older to determine if there was an overall difference in safety between these participants and younger participants.

Limited available postmarketing data suggest that individuals 65 years of age and older with one or more chronic medical conditions may have an increased risk for serious chikungunya-like illness following vaccination with IXCHIQ *[see Warnings and Precautions (5.2)]*.

11 DESCRIPTION

IXCHIQ (Chikungunya Vaccine, Live) is a solution for intramuscular injection. IXCHIQ is supplied as a vial of sterile, Lyophilized Antigen Component, Live, and a syringe of Sterile Water Diluent Component. The Lyophilized Antigen Component, Live, is reconstituted at the time of use with the accompanying Sterile Water Diluent Component to form IXCHIQ. The Lyophilized Antigen Component, Live, is a white to slightly yellowish powder. After reconstitution, IXCHIQ is a clear colorless to slightly yellowish solution.

IXCHIQ contains live, attenuated chikungunya virus (generated by reverse genetics from La Réunion strain LR-CHIKV clone LR2006 OPY1). The attenuated virus has a deletion in non-structural protein 3, which encodes a component of the viral replicase complex, and replicates less efficiently than the wild-type CHIKV. The vaccine virus is propagated in Vero cells (a continuous line of monkey kidney cells) in media containing amino acids, vitamins, minerals and fetal bovine serum. The viral harvests are pooled, clarified and concentrated. The virus is purified by chromatography and ultracentrifugation, mixed with formulation buffer and lyophilized.

After reconstitution, each approximately 0.5-mL dose contains not less than 3.0 $\log_{10}$ $TCID_{50}$ (Tissue Culture Infectious Dose 50%) of live, attenuated chikungunya virus. Each dose also contains 0.05 mg recombinant human albumin, 25 mg sucrose, 2.5 mg D-sorbitol, 0.75 mg L-methionine, 0.51 mg magnesium chloride hexahydrate, 3.68 mg trisodium citrate di-hydrate, 0.313 mg di-potassium hydrogen phosphate, and 0.098 mg potassium di-hydrogen phosphate. Each dose may contain residual amounts of Vero cell proteins (less than 5 ng/dose), Vero cell DNA (less than 10 pg/dose), bovine serum albumin (less than 500 pg/dose) and protamine sulphate (less than 1 mcg/dose), from the manufacturing process.

IXCHIQ does not contain a preservative.

The stoppers of the syringes containing Sterile Water Diluent Component and the stoppers of the vials containing Lyophilized Antigen Component, Live, are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The exact mechanism of protection has not been determined. IXCHIQ elicits CHIKV-specific immune responses.

12.2 Pharmacokinetics

Viremia and urinary shedding

Quantitative reverse transcription-polymerase chain reaction (qRT-PCR) was used to assess vaccine viremia in plasma and urinary shedding after vaccination on Days 1 (day of vaccination), 4, 8 and 15 in one Phase 1 study (NCT03382964). Participants were vaccinated with a single dose of one of three dose levels [low (3.5 $\log_{10}$ $TCID_{50}$/dose), medium (4.5 $\log_{10}$ $TCID_{50}$/dose), and high (5.5 $\log_{10}$ $TCID_{50}$/dose)] of a formulation containing the same attenuated CHIKV used in IXCHIQ. The amount of attenuated CHIKV in each medium dose was equivalent to the maximum amount in a dose of IXCHIQ. Viremia was not detected in any participant in any study arm on Day 1. The highest proportion of viremic participants was observed at the Day 4 time point (81%, 90%, and 95% in the low, medium, and high dose groups, respectively, Table 4.). Viremia had resolved in all participants by the Day 15 time point, including those who received the high dose formulation. The vaccine virus was detected in the urine of one participant in the low dose group on Day 8.

Table 4. Plasma Viremia on Days 4, 8 and 15 in participants vaccinated with a formulation containing attenuated CHIKV (Study NCT03382964)

Visit		Attenuated CHIKV Formulation		
		Low[1] Dose (N=31)	Medium[2] Dose (N=30)	High[3] Dose (N=59)
Day 4	Participants with quantifiable viremia, n/N (%)	25 / 31 (81%)	27 / 30 (90%)	56 / 59 (95%)
	Mean plasma viremia (GCE§/mL)	73,601	89,354	229,224
Day 8	Participants with quantifiable viremia, n/N (%)	6 / 31 (19%)	5 / 30 (17%)	4 / 59 (7%)
	Mean plasma viremia (GCE§/mL)	8814	15,725	27,028
Day 15	Participants with quantifiable viremia, n/N (%)	0 / 31 (0%)	0 / 30 (0%)	0 / 59 (0%)
	Mean plasma viremia (GCE§/mL)	N/A*	N/A*	N/A*

§ GCE = genome copy equivalent; * N/A = not applicable

Dose $TCID_{50}$: [1]low (3.5 $\log_{10}$ $TCID_{50}$/dose), [2]medium (4.5 $\log_{10}$ $TCID_{50}$/dose), [3]high (5.5 $\log_{10}$ $TCID_{50}$/dose)]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

IXCHIQ has not been evaluated for carcinogenic or mutagenic potential or impairment of male fertility. In a developmental toxicity study conducted in rats, there were no vaccine-related effects on female fertility *[see Use in Specific Populations (8.1)]*.

13.2 Animal Toxicology and/or Pharmacology

A passive transfer study was performed in non-human primates (NHPs) using human anti-CHIKV immune sera collected from a Phase 1 study (NCT03382964). In the Phase 1 study, participants received a single dose of a vaccine formulation containing the same attenuated CHIKV used in IXCHIQ. Sera obtained between Days 14 and 180 after vaccination were pooled to generate 8 serum pools representing varying anti-CHIKV neutralizing

antibody titers. In the passive transfer study, 40 CHIKV-naïve cynomolgus macaques (*M. fascicularis*) were administered human anti-CHIKV immune sera from the 8 serum pools (n=5 per group) and 6 CHIKV-naïve cynomolgus macaques were administered non-immune control sera by intravenous injection. One day after the transfers, serum samples were obtained from the macaques to determine pre-challenge anti-CHIKV neutralizing antibody titers by $\mu PRNT_{50}$ assay. Animals were challenged with 100 times the 50% animal infectious dose of wild-type CHIKV strain La Réunion 2006-OPY1, corresponding to 7,000–10,000 Plaque Forming Units.

Animal monitoring included assessment of wild-type CHIKV-induced viremia by RT-qPCR and body temperature through 14 and 28 days after challenge, respectively. None of the animals receiving post-vaccination serum pools developed fever after the challenge. Fever and viremia within 7 days post-challenge were detected in all 6 macaques receiving non-immune human sera. Data from the NHP study were analyzed by logistic regression and a µPRNT50 titer of ≥150 was determined to be reasonably likely to predict clinical benefit in the Phase 3 study.

14 CLINICAL STUDIES

IXCHIQ effectiveness against disease caused by CHIKV was based on an evaluation of seroresponse defined as an anti-CHIKV neutralizing antibody level above a threshold ($\mu PRNT_{50}$ titer ≥150). This threshold was derived from a non-human primate model [see *Nonclinical Toxicology (13.2)*].

The seroresponse rate 28 days after a single dose of IXCHIQ is presented in Table 5.

Table 5. Seroresponse Rates 28 Days Post-Vaccination as Determined by µPRNT Assay, in Study 1 (PP Population)

IXCHIQ	Placebo
N=266	**N=96**
% (n) [95%CI]	**% [95%CI]**
98.9 (263) [96.7, 99.8]*	0 [0.0, 3.8]

Abbreviations: CI=confidence interval; µPRNT=micro plaque reduction neutralization test; PP=per-protocol (population).
*Success criterion: lower bound of the 95% confidence interval for seroresponse rate >70%.

The seroresponse rate 180 days after a single dose of IXCHIQ was 96.3% (95% CI: 93.1, 98.3).

15 REFERENCES

1. Gérardin P, Barau G, Michault A, Bintner M, Randrianaivo H, Choker G, et al. Multidisciplinary prospective study of mother-to-child chikungunya virus infections on the island of La Réunion. PLoS Med. 2008;5(3):0413–2

16 HOW SUPPLIED/STORAGE AND HANDLING

IXCHIQ is supplied in a carton (NDC 42515-003-01) containing:

- one single-dose vial of Lyophilized Antigen Component, Live (NDC 42515-004-01)
- one prefilled ungraduated syringe of Sterile Water Diluent Component (NDC 42515-005-01) (packaged without needles).

Store vial of Lyophilized Antigen Component, Live, and syringe of Sterile Water Diluent Component in a refrigerator at 2°C to 8°C (35°F to 46°F). Store in the original carton to protect from light. DO NOT FREEZE.

17 PATIENT COUNSELING INFORMATION

Advise the vaccine recipient to read the FDA-approved patient labeling (Patient Information).

Question the vaccine recipient about reactions to previous vaccines.

Inform the vaccine recipient of the benefits and risks of IXCHIQ, including:

- the potential for serious, severe or prolonged chikungunya-like illness *[See Warnings and Precautions (5.2)]*, and
- the potential for vertical transmission of vaccine virus from pregnant individuals and potential fetal/neonatal adverse reactions *[See Warnings and Precautions (5.3)]*.

Advise the recipient that IXCHIQ may not protect everyone who gets the vaccine and that personal precautions should be taken to reduce exposure to mosquito bites (e.g., adequate clothing, use of repellents, mosquito nets).

There is a pregnancy exposure registry for IXCHIQ. Encourage individuals exposed to IXCHIQ around the time of conception or during pregnancy to register by calling 1-855-417-6214 or by visiting www.valneva-oxon.com/IXCHIQPregnancyRegistry *[See Use in Specific Populations (8.1)]*.

Advise vaccine recipient to report any adverse reactions to their healthcare provider or to the Vaccine Adverse Event Reporting System (VAERS) at 1-800-822-7967 and www.vaers.hhs.gov.

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Patient Information

IXCHIQ (pronounced "ĭks-chēk")

Generic name: chikungunya vaccine, live

Read this information about IXCHIQ before you are vaccinated. If you have any questions about IXCHIQ after reading this leaflet, ask your healthcare provider. This leaflet does not take the place of talking with your healthcare professional about IXCHIQ. Only your healthcare provider can decide if IXCHIQ is right for you.

What is IXCHIQ?

- IXCHIQ is a vaccine for use in individuals 18 years of age and older who are at high risk of exposure to chikungunya virus to help protect against chikungunya virus disease.
- You should still protect yourself from mosquito bites even if you have received the IXCHIQ vaccine.
- IXCHIQ may not fully protect everyone who gets the vaccine.
- IXCHIQ does not protect against other diseases transmitted by mosquitoes.

Who should not get IXCHIQ?

You should not get IXCHIQ if you:
- have a weakened immune system due to certain conditions or therapy.
- have ever had a severe allergic reaction to any of the ingredients in the vaccine. A list of ingredients can be found at the end of this leaflet.

IXCHIQ is not approved for use in individuals below the age of 18 years.

What should I tell my healthcare professional before I am vaccinated with IXCHIQ?

It is very important to tell your healthcare provider if you:
- have had an allergic reaction to any ingredient of IXCHIQ.
- have a bleeding disorder or are on a blood thinner.
- have a weakened immune system due to a condition or therapy.
- have any chronic (long-term) medical conditions.
- are or may be pregnant, or are breast feeding.
- currently have any illness with a fever of more than 38.0 °C (100.4 °F).
- take any medicines, even those you can buy over the counter.

How is IXCHIQ given?

IXCHIQ is given as an injection into the muscle.

What are the risks of IXCHIQ?

IXCHIQ commonly causes symptoms similar to those experienced by people who have chikungunya disease (e.g., fever, headache, fatigue, muscle pain and joint pain). These symptoms typically begin within the first two weeks after receiving IXCHIQ. In some people who receive IXCHIQ, these symptoms may prevent daily activity,

require medical intervention including hospitalization, and last for weeks or months.
Some people who have received IXCHIQ have experienced serious side effects similar to complications that can occur with chikungunya. Serious side effects that have been reported include:

- Abnormal heart rhythm
- Rapid heart rate
- Aseptic meningitis (inflammation of the membranes covering the brain and spinal cord that is not due to a bacterial infection)
- Encephalopathy (brain dysfunction with symptoms such as confusion and impaired memory)
- Encephalitis (inflammation of brain tissue) that resulted in death

People 65 years of age and older who have one or more chronic (long-term) medical conditions might have an increased risk for these types of serious side effects after receiving IXCHIQ.

In some people IXCHIQ causes a decrease in the numbers of white blood cells. This usually occurs within the first week following vaccination. In most people, the numbers of white blood cells return to normal on their own within one month.

The most common side effects of IXCHIQ are headache, fatigue, muscle pain, joint pain, fever, tenderness at the injection site and nausea.

These are not all of the possible side effects of IXCHIQ. You can ask your healthcare provider about other side effects that have been reported.

Contact your healthcare provider right away if you get any symptoms that concern you after receiving IXCHIQ.

Tell your healthcare provider if you have any of the following problems after receiving IXCHIQ because these may be signs of an allergic reaction:

- difficulty breathing
- hoarseness or wheezing
- hives
- dizziness, weakness or fast heart beat

You may report side effects to the Vaccine Adverse Event Reporting System (VAERS) at 1-800-822-7967 or https://vaers.hhs.gov.

What are the ingredients of IXCHIQ?

IXCHIQ contains weakened live chikungunya virus (CHIKV), recombinant human albumin, sucrose, D-sorbitol, L-methionine and salts. IXCHIQ may contain trace amounts of bovine serum albumin, Vero cell protein, Vero cell DNA and protamine sulphate.

What else should I know about IXCHIQ?

This leaflet is a summary of information about IXCHIQ. If you would like more information, please talk to your healthcare provider.

Month/YYYY

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