PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

IXCHIQ

Chikungunya Vaccine, live, attenuated

Powder for Solution for Intramuscular Injection

Not less than 3.0 log10 TCID50/0.5mL

Anatomical Therapeutic Chemical (ATC)

Active immunization agent

Valneva Austria GmbH
Campus Vienna Biocenter 3
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Austria

Imported by:
Quality & Compliance Services Inc.
Mississauga
ON L5N 1V8

Manufactured for:
Valneva Canada Inc.
Kirkland
QC H9H 5B9

Date of Initial Authorization:
JUN 20, 2024

Submission Control Number: 275762

RECENT MAJOR LABEL CHANGES

Not applicable.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

IXCHIQ (chikungunya vaccine, live, attenuated) Powder for Solution for Intramuscular Injection is a live-attenuated vaccine, intended for active immunization in individuals 18 years and older for the prevention of disease caused by the chikungunya virus (CHIKV), as a single-dose immunization.

1.1 Pediatrics

The safety and immunogenicity of IXCHIQ have not been established in individuals under 18 years of age. Therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Clinical studies of IXCHIQ include participants 65 years of age and older and their data contribute to the overall assessment of safety and immunogenicity.

2 CONTRAINDICATIONS

IXCHIQ is contraindicated in:

- Individuals with a history of immunodeficiency (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).
- Patients who are hypersensitive to this vaccine or to any ingredient in the formulation or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Pregnancy. Women of child-bearing potential should be advised to avoid pregnancy for one month following vaccination (see also 7 WARNINGS AND PRECAUTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

For intramuscular injection only.

4.2 Recommended Dose and Dosage Adjustment

One single dose of IXCHIQ, which is 0.5 mL after reconstitution.

4.3 Reconstitution

Reconstitute the Lyophilized IXCHIQ Powder only with the accompanying Sterile Water Diluent. The reconstituted vaccine is a clear, colorless to slightly yellowish liquid solution [See 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING]. The reconstituted vaccine should be inspected visually for particulate matter and discoloration prior to administration. If either of these conditions exists, do not administer the vaccine. Follow the figure descriptions below for preparation.

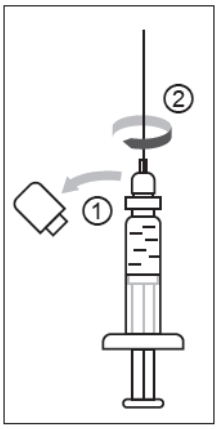

Figure 1

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

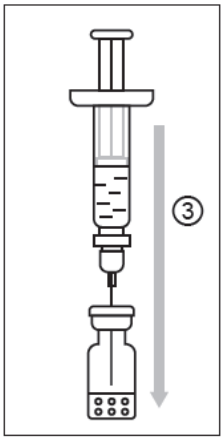

Figure 2

3) Cleanse the stopper of the vial of Lyophilized Powder. Slowly transfer the entire content of the prefilled syringe of diluent into the vial containing lyophilized powder.

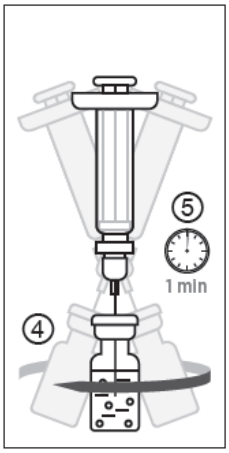

Figure 1

4) Gently swirl the vial to dissolve the lyophilized IXCHIQ. Avoid strong shaking or inverting of the vial.
5) Wait for at least one minute for complete reconstitution of the vaccine.

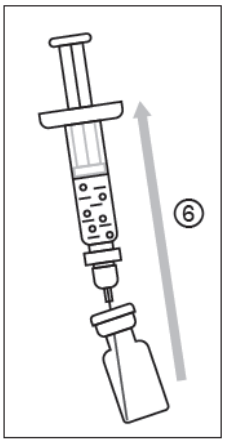

Figure 2

6) After reconstitution, slightly tilt the vial to withdraw the entire contents of the reconstituted IXCHIQ into the same syringe. Avoid inverting the vial.

   Changing needles between withdrawing the vaccine from the vial and injecting it into a recipient is not necessary unless the needle has been damaged or contaminated.

   Dispose of used sharps and needles according to your local requirements.

4.4 Administration

Administer the reconstituted IXCHIQ vaccine intramuscularly (i.m.) into the deltoid muscle immediately. If not used immediately, store the reconstituted vaccine at room temperature and administer within 30 minutes.

Discard vaccine if not used within 30 minutes.

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

Immunity following Chikungunya virus infection is thought to convey lifelong immunity. The need for a booster dose following immunization with the live-attenuated vaccine has not been established.

4.5 Missed Dose

Not applicable.

5 OVERDOSAGE

No case of overdose has been reported with IXCHIQ. In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular	Powder for Solution for Injection/ Each 0.5 mL dose of the vaccine contains not less than 3.0 $\log_{10}$ $TCID_{50}$ of live attenuated chikungunya virus.	D-Sorbitol (0.5% (w/w)), L-Methionine (10 mM), Magnesium Chloride (5 mM), Potassium Phosphate (5 mM), Recombinant Human Albumin (rHA) (0.01%), Sucrose (5% (w/w)), Trisodium citrate di-hydrate (25 mM)

IXCHIQ is supplied as a single-dose vial of lyophilized powder to be reconstituted with the supplied prefilled syringe of diluent (sterile water for injection). A single dose is 0.5 mL after reconstitution. Each 0.5 mL dose of the vaccine contains not less than 3.0 log10 TCID50 of live attenuated chikungunya virus.

The appearance of the lyophilized vaccine prior to reconstitution is white to slightly yellowish homogeneous powder. After reconstitution, the solution is a clear, colorless to slightly yellow.

7 WARNINGS AND PRECAUTIONS

General

As with other vaccines, vaccination with IXCHIQ should be postponed in individuals suffering from an acute severe febrile illness or infection.

Syncope (fainting) can occur following, or even before, any vaccination as a vasovagal response to the needle injection, in the context of an anxiety-related reaction. It is important that procedures are in place to avoid injury from fainting.

Vaccination with IXCHIQ may not protect all individuals. It is recommended to continue personal protection measures against mosquito bites after vaccination.

Acute Allergic Reactions

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

Driving and Operating Machinery

No studies on the effects of IXCHIQ on the ability to drive and use machines have been performed. Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Hematologic

As with other vaccines administered intramuscularly, IXCHIQ should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an

intramuscular administration to these individuals.

Immune-mediated Arthritis

Available data in adults with a history of immune-mediated or clinically relevant arthritis are not sufficient to determine the safety of IXCHIQ, as this condition was an exclusion criterion for participation in clinical trials.

Reproductive Health: Female and Male Potential

- **Fertility**

Reproductive and developmental toxicology of IXCHIQ was conducted in a single pre- and post-natal developmental toxicity study in pregnant rats which did not identify significant adverse effects in female fertility (See 16. NON-CLINICAL TOXICOLOGY AND PHARMACOLOGY section). No studies in male fertility were conducted.

- **Teratogenic Risk**

Reproductive and developmental toxicology of IXCHIQ was conducted in a single pre- and post-natal developmental toxicity study in pregnant rats which did not identify significant adverse effects in fetal examination (See 16. NON-CLINICAL TOXICOLOGY AND PHARMACOLOGY section).

7.1 Special Populations

7.1.1 Pregnant Women

Women of child-bearing potential should be advised to avoid pregnancy for one month following vaccination. Available data in pregnant women are not sufficient to determine the safety of IXCHIQ regarding pregnancy, embryofetal development, parturition and postnatal development.

No adequate and well-controlled studies of IXCHIQ have been performed among pregnant women. Human data available from clinical trials with IXCHIQ are insufficient to establish the presence or absence of vaccine-associated risk during pregnancy. One developmental toxicity study was performed in female rats, see 16 NON-CLINICAL TOXICOLOGY.

Disease-associated maternal and/or embryo/fetal risk

Vertical transmission of CHIKV from mothers with viremia at delivery to their infants has been reported and can cause severe, potentially fatal neurological disease in neonates.

Fetal/neonatal adverse reactions

Vaccine viremia can occur 3 to 7 days after vaccination and is resolved by 14 days after vaccination [See 10.3 Pharmacokinetics]. The potential for transmission of the vaccine virus from mother to infant is unknown.

Pregnancy Exposure

Women who received IXCHIQ during pregnancy are encouraged to report any suspected exposure or adverse reactions to Valneva Canada, or ask their healthcare professional to do so, at 1-855-356-0831

7.1.2 Breast-feeding

It is unknown if IXCHIQ is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk.

One developmental toxicity study performed in rats showed IXCHIQ-specific antibodies in the milk of vaccinated female rats from day 5 of lactation.

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. Vaccine viremia can occur 3 to 14 days after vaccination and is resolved by 14 days after vaccination [See 10.3 Pharmacokinetics]. The potential for transmission of the vaccine virus from mother to infant through breastmilk is unknown. To date, no infants have been found to be infected with CHIKV or vaccine virus through breastfeeding. 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.

7.1.3 Pediatrics

The safety and immunogenicity of IXCHIQ in children and adolescents under 18 years of age have not yet been established. Therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Clinical studies of IXCHIQ include participants 65 years of age and older and their data contribute to the overall assessment of safety and immunogenicity (see 8 ADVERSE REACTIONS and 14 CLINICAL).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In clinical study VLA1553-301, the most common solicited injection site reaction (>10%) was tenderness (10.6%). The most common solicited systemic adverse reactions (>20%) were headache (31.6%), fatigue (28.5%), and myalgia/muscle pain (23.9%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety profile of IXCHIQ was evaluated from data generated from 3 randomized, multicenter clinical studies (VLA1553-301, VLA1553-302, and VLA1553-101) all conducted in North America in healthy adult participants 18 years of age and older. Study VLA1553-101 was done using an earlier formulation and was a supportive dose-escalation Phase I trial of IXCHIQ in 120 participants. Study VLA1553-301 was the pivotal double-blind placebo-controlled Phase III trial in 4,115 participants who received IXCHIQ or placebo (phosphate buffered saline or PBS) as a single dose. Study VLA1553-302 was a supportive non-placebo-controlled Phase III trial investigating the consistency of three lots of IXCHIQ given as a single dose in 408 participants.

The IXCHIQ safety data described herein were collected in 4,115 participants from the main VLA1553-301 clinical trial, randomized 3:1 to receive IXCHIQ or PBS (placebo). A total of 3,082 healthy adults 18 through 88 years of age received a single dose of IXCHIQ and 1,033 received placebo. Participants were followed-up for safety for 6 months post-vaccination. Overall, 54.7% of participants were female. Ethnicity was reported as 80.4% White, 13.9% Black or African American, 1.7% Asian, 0.8% American Indian/Alaska Native, 0.4% Native Hawaiian/Pacific Islander and 2.8% as other. The IXCHIQ and placebo groups were similar with regard to demographics.

Solicited Adverse Reactions

Solicited systemic and injection site adverse reactions were reported within 10 days after vaccination in main study, VLA1553-301, reported by the participant in the Participant eDiary and were recorded on the AE (adverse event) page of the electronic case report form. Overall, 1,553/3,082 (50.4%) of IXCHIQ recipients vs 279/1,033 (27.0%) of placebo recipients experienced at least one solicited systemic adverse reaction. The most common systemic adverse reactions (>20%) were headache (31.6%), fatigue (28.5%) and myalgia (23.9%), of these most (>95%) were mild to moderate. Overall, 463/3,082 (15.0%) of IXCHIQ recipients vs 115 (11.1%) of placebo recipients experienced at least one injection site adverse reaction. The most common injection site adverse reaction (>10%) was tenderness (10.6%). Local and systemic adverse reactions resolved with a median duration of 2 days.

Solicited systemic adverse reactions and solicited injection site adverse reactions reported post-vaccination by trial participants via eDiary are provided in Table 2 below.

Table 2: Solicited Systemic and Injection Site Adverse Reactions Within 10 Days After a Single Vaccination (Safety Population in Study VLA1553-301)

Adverse Reaction Category	**Study VLA1553-301**	
	IXCHIQ (N=3,082) n (%)	**Placebo (PBS)** (N=1,033) n (%)
Any Solicited Adverse Reactions	**1634 (53.0)**	**332 (32.1)**
Solicited Systemic Adverse Reactions	**1,553 (50.4)**	**279 (27.0)**
Headache	973 (31.6)	152 (14.7)
Fatigue	879 (28.5)	131 (12.7)
Myalgia/Muscle Pain	737 (23.9)	76 (7.4)
Arthralgia/Joint Pain	529 (17.2)	51 (4.9)
Fever (≥ 38° C)	415 (13.5)	9 (0.9)
Nausea	345 (11.2)	58 (5.6)
Rash	70 (2.3)	5 (0.5)
Vomiting	59 (1.9)	10 (1.0)
Solicited Injection Site Adverse Reactions	**463 (15.0)**	**115 (11.1)**
Tenderness	328 (10.6)	84 (8.1)

Adverse Reaction Category	Study VLA1553-301	
	IXCHIQ (N=3,082) n (%)	**Placebo (PBS)** (N=1,033) n (%)
Pain	191 (6.2)	38 (3.7)
Erythema/Redness	46 (1.5)	15 (1.5)
Induration	44 (1.4)	8 (0.8)
Swelling	21 (0.7)	8 (0.8)

All solicited injection site adverse reactions were graded as mild or moderate in severity, except for a single solicited injection site adverse reaction of pain graded as severe in the IXCHIQ group.

Chikungunya-Like Adverse Reactions

In Study VLA1553-301, participants were monitored for a cluster of symptoms consistent with wild-type chikungunya infection. Chikungunya-like adverse reactions were defined as fever (≥38 °C) 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, regardless of whether they occurred simultaneously or not. Severe chikungunya-like adverse reactions included symptoms that prevented daily activity and/or required medical intervention.

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

Table 3. Frequency of Symptoms Among Participants With Chikungunya-Like Adverse Reactions (Study VLA1553-301)

Chikungunya-Like Symptom	**IXCHIQ** (N=361) n (%)
Pyrexia (any)	361 (100)
Headache (any)	280 (77.6)
Fatigue (any)	264 (73.1)
Myalgia (any)	215 (59.6)
Arthralgia (any)	159 (44.0)
Chills (any)	29 (8.0)
Rash (any)	22 (6.1)
Back pain (any)	13 (3.6)
Lymphadenopathy (any)	9 (2.5)

Dizziness (any)	6 (1.7)
Pain (any)	4 (1.1)
Paresthesia (any)	3 (0.8)
Hyperhidrosis (any)	2 (0.6)
Edema peripheral (any)	2 (0.6)
Asthenia (any)	1 (0.3)
Ataxia (any)	1 (0.3)
Atrial fibrillation (any)	1 (0.3)
Feeling abnormal (any)	1 (0.3)
Hypoesthesia (any)	1 (0.3)
Influenza like illness (any)	1 (0.3)
Neuropathy peripheral (any)	1 (0.3)
Rash erythematous (any)	1 (0.3)
Syncope (any)	1 (0.3)

n=number of participants with chikungunya-like adverse reactions.

The median onset of chikungunya-like adverse reactions in IXCHIQ recipients was 3 days (range 0 to 10 days) after vaccination. The median duration of chikungunya-like reactions in IXCHIQ recipients was 4 days (range 1 day to at least 6 months).

Twenty-two IXCHIQ recipients had prolonged chikungunya-like adverse reactions lasting longer than 14 days (median duration 33 days, range 15 days to at least 6 months) and 15 IXCHIQ recipients had chikungunya-like adverse reactions lasting longer than 28 days (median duration 94 days, range 29 days to at least 6 months).

Prolonged fatigue, myalgia, or headache (lasting longer than 14 days) were reported by 13 participants (nine of these participants had symptoms lasting longer than 28 days).

Prolonged arthralgia (lasting longer than 14 days) was reported by seven participants (five of these participants had arthralgia lasting longer than 28 days), 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.

Additionally, a 62-year-old female with no recorded fever developed intermittent polyarthritis involving fingers for more than 8 months, including development of a trigger finger requiring surgical release 4-5 months after vaccination.

Unsolicited Adverse Events

In Study VLA1553-301, unsolicited adverse events (AEs) that occurred within 28 days post-vaccination were reported overall in 21.8% of 3,082 participants receiving IXCHIQ compared with 13.3% of 1,033 participants receiving placebo. Overall, most unsolicited AEs were graded as mild or moderate. Eighteen participants (0.6%) in the IXCHIQ arm and six (0.6%) in the placebo arm experienced at least

one unsolicited AE that was graded severe. Unsolicited AEs were significantly more frequently considered related to the vaccination in the IXCHIQ arm (9.2% participants) than in the placebo arm (3.7% participants). Specific categories of unsolicited AEs are presented in Table 4 below.

Table 4. Unsolicited Adverse Events Within 28 Days After a Single Vaccination With a Frequency ≥1% in at Least One Study Arm (Safety Population in Study VLA1553-301)

Preferred Term (PT)	IXCHIQ (N=3,082) n (%)	Placebo (N=1,033) n (%)
Any Unsolicited Adverse Events	**671 (21.8)**	**137 (13.3)**
Back pain	35 (1.1)	6 (0.6)
Chills	57 (1.8)	2 (0.2)
Diarrhoea	43 (1.4)	4 (0.4)
Headache	27 (0.9)	12 (1.2)
Neutropenia	34 (1.1)	1 (0.1)

Serious Adverse Events

The proportions of participants who reported at least 1 serious adverse event within 6 months following administration was 1.5% (46/3,082) in the IXCHIQ group and 0.8% (8/1,033) in the placebo group. Overall, there were two serious adverse events (2/3,082 [0.1%]) requiring hospitalization that were considered to be related to IXCHIQ: 1 event of myalgia, and 1 event of hypovolemic hyponatremia and atrial fibrillation, both events showed full recovery.

A 58-year-old female with a history of fibromyalgia experienced severe myalgia, mild arthralgia, tachycardia and tachypnea, with onset 1 to 2 days after vaccination, was hospitalized 3 days after vaccination for 7 days, and fully recovered; myalgia resolved after 30 days.

A 66-year-old male experienced severe fever for 7 days, starting 4 days post-vaccination; he was hospitalized 9 days post-vaccination for 3 days 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.

There were no serious adverse events reported in the placebo group.

Deaths and Adverse Events leading to Withdrawal from Study

Three participants died during Study VLA1553-301 due to events independent of study procedures (coronary artery disease, COVID-19, and anoxic brain injury). None of the deaths was considered as related to IXCHIQ. Approximately 0.1% of participants who received IXCHIQ versus 0.2% in the placebo group discontinued their trial participation due to adverse events.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Participants 17 years of age or younger were excluded from clinical trials with IXCHIQ.

8.3 Less Common Clinical Trial Adverse Reactions

Less common related, unsolicited adverse events, included:

Gastrointestinal: Diarrhoea.
General Disorders: Chills.
Haematologic Disorders: Neutropenia, leukopenia.
Immune system Disorders: Lymphadenopathy
Musculoskeletal and Connective Tissue Disorders: Back pain
Nervous System Disorders: Dizziness

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

In Study VLA1553-301, laboratory data were collected at 7, 28, 84 and 180 days post-vaccination in the immunogenicity subset. Most hematology, chemistry and coagulation parameters were generally well balanced between the IXCHIQ and placebo arms. The exception were abnormal white cell counts, specifically leukocytes (all types of white blood cells), neutrophils and lymphocytes; which were more frequently observed in the IXCHIQ recipients compared with placebo recipients (see Table 5). Most of the abnormal hematology parameters were of mild severity (grade 1): IXCHIQ arm 19.1% to 27.6% and placebo arm 5.8% to 11.6%. Of 186 participants with abnormal cell counts at the 7-day post-vaccination assessment, 92% (171/186) had available hematology results at the 28-day post-vaccination assessment, of which 88% (150 /171) were in the normal range.

Table 5. Abnormal Hematology Results by Maximum Grade Post-vaccination (Immunogenicity Subset in Study VLA1553-301)

Laboratory Parameter	**IXCHIQ**[a] (N=372) n (%)	**Placebo**[a] (N=125) n (%)
Leukocytes	116 (32.0)	7 (5.8)
Neutrophils	153 (42.3)	15 (12.4)
Lymphocytes	85 (23.5)	9 (7.4)

Percentages are based on the number of individuals with at least one postbaseline result.

Three IXCHIQ recipients reported other significant non-serious severe adverse events: two events of neutropenia lasting for 13 or 20 days (both events were considered to be related to IXCHIQ) and one event of lymphopenia lasting for 22 days (the event was considered not related to IXCHIQ). All events resolved within 28-day post-vaccination.

Overall, changes in clinical laboratory test results were considered expected and consistent with a normal physiologic response to a live-attenuated viral vaccine.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Data are not available to establish the safety and immunogenicity of concomitant administration of

IXCHIQ with other vaccines.

9.7 Drug Laboratory Test Interactions

Any laboratory testing within 2 weeks post-vaccination with IXCHIQ may result in transient abnormalities in results, especially among hematology parameters.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The exact mechanism of protection has not been determined. IXCHIQ elicits CHIKV-specific immune responses against all globally circulating chikungunya virus (CHIKV) genotypes.

10.2 Pharmacodynamics

Clinical studies with IXCHIQ included immunogenicity assessments to characterize the immune response to IXCHIQ. Immunogenicity endpoints were used as surrogate endpoints supporting the evaluation of clinical efficacy (see 13 CLINICAL TRIALS).

10.3 Pharmacokinetics

Viremia: The phase I study (Study VLA1553-101) assessed the kinetics of vaccine viremia on Day 3, Day 7 and Day 14 following single vaccination with IXCHIQ at three intramuscular dose levels ($3.2x10^3$ $TCID_{50}$, $3.2x10^4$ $TCID_{50}$, and $3.2x10^5$ $TCID_{50}$) in heathy adults (see 14 CLINICAL TRIALS). The middle dose ($3.2x10^4$ $TCID_{50}$ or 4.5 log10 $TCID_{50}$) is within the approved dose range (3.6 - 4.6 log_{10} $TCID_{50}$) of IXCHIQ. The viral titer in all study groups was the highest on Day 3, sharply dropped by about 85% on Day 7 and became undetectable on Day 14. The plasma viral titer was vaccine dose-dependent with mean viral RNA titer at 73,601.2 GCE/mL, 89,353.7 GCE/mL and 229,224.1 GCE/mL on Day 3 following vaccination at the three ascending dose level, respectively. Note: the administrated viral doses are too low to be detectable in plasma if the virus does not replicate in the body.

One participant shed virus in urine in the low dose group on Day 7.

11 STORAGE, STABILITY AND DISPOSAL

Store vial with lyophilized powder and diluent in a refrigerator at 2°C to 8°C. DO NOT FREEZE. Do not use the vaccine after the expiration date shown on the vial label. Store in the original package.

After reconstitution, administer IXCHIQ immediately. If not used immediately, store the reconstituted vaccine at room temperature and administer within 30 minutes. DO NOT FREEZE RECONSTITUTED VACCINE.

Discard reconstituted vaccine, if not used within 30 minutes.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Live Attenuated chikungunya La Reunion strain (LR-CHIKV clone LR2006 OPY1)

Product Characteristics:

IXCHIQ, chikungunya vaccine, live-attenuated, is a lyophilized powder reconstituted with sterile water to form a sterile solution for intramuscular injection. Each 0.5 mL dose of the vaccine contains not less than 3.0 $\log_{10}$ $TCID_{50}$ of live attenuated chikungunya virus.

The vaccine is produced in Vero cells. Viral harvests are pooled, clarified, concentrated and purified. The purified virus solution is further sterile filtered, aliquoted and stored at deep frozen conditions until formulation. The Vero cells, Viral Harvests, Drug Substance and Excipients used in manufacturing are all tested to provide assurance that the final product is free of potential adventitious agents.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 3: Summary of patient demographics for clinical trials for IXCHIQ

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex (%)
VLA1553-301	Double-blind, randomized placebo-controlled	IXCHIQ 1×10^4 TCID50 per 0.5 mL, or placebo (phosphate buffered saline, PBS) Intramuscular injection Single dose, 6 month follow up	IXCHIQ: 3,093 (3,045 planned) Immunogenicity subset: 375 Placebo: 1,035 (1,015 planned) Immunogenicity subset: 126	45.0 years (18.0-94.0)	1,864 M (45.3%) 2,251 F (54.7%)

Study VLA1553-301 enrolled healthy adult men and women without prior known or suspected CHIKV infections and unlikely to become exposed to CHIKV during the study. Subjects with chronic illnesses or conditions that were stable and well controlled on therapy for the past 6 months were eligible to participate in the clinical studies. Immuno-compromised subjects were not eligible to participate in the clinical study.

14.2 Study Results

Seroresponse was selected as a surrogate immunogenicity endpoint of efficacy. It is defined as achieving a virus neutralizing antibody µPRNT50 titer ≥150, which was considered to predict a clinical benefit. This is based on nonclinical data from a non-human primate pharmacology study showing that animals treated with immune sera from clinical samples collected in Study VLA1553-101 were protected against mild CHIKV disease induced by challenge with a WT CHIKV strain (See Study VAC1816 02 in 16. NON-CLINICAL TOXICOLOGY AND PHARMACOLOGY). Pre challenge neutralizing antibody titer level about 150 resulted in undetectable virus during 14 days after the challenge.

In Study VLA1553-301, the primary immunogenicity endpoint was the seroresponse rate (proportion of participants who had seroresponse in a study group) at 28 days post-vaccination. Key secondary immunogenicity endpoint was immune response as measured by CHIKV-specific neutralizing antibody titers on Day 8, Day 29, Day 85, and at Month 6 post-vaccination as determined by µPRNT assay.

Seroresponse Rate

The seroresponse rate 28 days post-vaccination after a single dose of IXCHIQ is presented in Table 4.

Table 4: Seroresponse Rates 28 days post-vaccination, as Determined by µPRNT Assay, in Study VLA1553-301 (PP Population)

Study	**Study VLA1553-301**	
Treatment	**Placebo**	**IXCHIQ**
	N=96	**N=266**
	(n (%) [95%CI])	**(n (%) [95%CI])**
Day 29 (28 days post-vaccination)	0 (0) [0.0, 3.8]	263 (98.9) [96.7, 99.8]*

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).

Geometric Mean Titer (GMT)

The geometric mean titer 28 days and 6 months post-vaccination after a single dose of IXCHIQ is presented in Table 5.

Table 5: GMT of CHIKV specific Neutralizing Antibodies on 28 days and 6 months post-vaccination, as Determined by µPRNT Assay, in Study VLA1553-301 (PP Population)

Study	Study VLA1553-301	
Treatment	**Placebo**	**IXCHIQ**
	N=96	**N=266**
Day 29 (28 days post-vaccination)	10.1	3,361.6
Day 180 (6 months post-vaccination)	10.0	752.1

Abbreviations: CHIKV=chikungunya virus; GMT=Geometric Mean Titer; µPRNT=micro plaque reduction neutralization test; PP=per-protocol (population).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY AND PHARMACOLOGY

Animal Toxicology Studies

One repeat dose toxicity study in rabbits and one pre- and post-natal developmental study in female Sprague-Dawley rats (see below) were conducted in animal toxicology studies to investigate the safety of IXCHIQ vaccine. There were no significant safety issues identified in these studies. However, unlike humans, rats and rabbits have strong natural resistance against CHIVK infection.

General Toxicology: In a repeat dose toxicity study, the intramuscular injection of 3.8×10^5 $TCID_{50}$/dose of IXCHIQ to rabbits on 2 occasions at a 2-week interval was well-tolerated both systemically and locally. IXCHIQ was associated with an inflammatory response and reactions at the administration sites. The findings resolved after a 30-day recovery.

Carcinogenicity: IXCHIQ has not been evaluated for carcinogenic potential.

Genotoxicity: IXCHIQ has not been evaluated for mutagenic potential.

Reproductive and Developmental Toxicology

The effect of IXCHIQ vaccine on female fertility, reproductive performance, and pre-/post-natal development was evaluated in one pre- and post-natal developmental toxicity study using pregnant rats. The animals were intramuscularly administered with IXCHIQ (1.9×10^4 $TCID_{50}$/rat or 4.3 log10 $TCID_{50}$/rat) or placebo once 15 days prior to gestation and once on gestation Day 6. No significant adverse effects on mating, fertility, pregnancy, parturition, lactation, embryo-fetal or pre-weaning development were observed except that the rate of post-implantation loss in IXCHIQ-treated animals in the littering phase was statistically higher than that in placebo control animals but within the history range of the parameter obtained in the testing facility.

Pharmacology Studies in Non-human Primates (NHPs)

A study in non-human primates, *Macaca fascicularis*, (Study PHY1802-02) compared viral replication, viral shedding, presence of viral RNA in relevant tissues, inflammatory responses, and clinical impacts between IXCHIQ and its wild-type (WT) CHIKV parent strain, LR2006-OPY1, following the same

intramuscular dose of 3.2 x 10^6 $TCID_{50}$. This dose is vastly higher than the estimated maximum amount of CHIKV that one CHIKV-vector mosquito may deliver to human. The kinetic profiles of plasma viremia were similar for WT CHIKV and IXCHIQ with viral titers peaking on day 2 and dropping by >99.9% (about 4.2 logs) until day 6 after virus injection. However, the geometric mean peak titer for IXCHIQ was reduced by about 99.8% (2.8 logs) compared to that for WT CHIKV, indicating that replication of IXCHIQ in the NHPs was attenuated by about 99.8% compared to that of its parent WT CHIKV strain. The WT CHIKV-treated animals experienced fever and lymphopenia, the hallmarks of CHIKV illness, but only in mild to moderate severity and a short duration. Despite being heavily attenuated in replication in the animals compared to WT CHIKV, IXCHIQ induced fever and lymphopenia in a similar or slightly lesser extent in severity and/or duration, if any, compared to those seen in the WT CHIKV-treated animals.

A non-human primate pharmacology study (Study VAC1816 02) investigated protective effects of pooled human sera from IXCHIQ -vaccinated subjects in the Phase I clinical study (VLA1553-101) against CHIKV infection induced by challenge with WT CHIKV strain LR2006-OPY1. Challenge with a subcutaneous dose (1.5×10^4 $TCID_{50}$) of WT CHIKV in the animals resulted in a significant level of plasma viremia with a geometric mean peak titer of 1.3×10^9 GCE/ml but only induced mild clinical signs of chikungunya disease, i.e. mild fever and lymphopenia with short duration (less than 2 days for lymphopenia). Intravenous transfer of pooled sera of IXCHIQ -vaccinated subjects in the Phase I clinical study (VLA1553-101) in the animals provided protection against CHIKV infection induced by subsequent challenge of WT CHIKV. In the animals who had plasma human CHIKV-specific neutralizing antibody titer around 150 $\mu PRNT_{50}$, there was no detectable plasma CHIKV RNA, no clinical signs of chikungunya disease including fever or modification of blood parameters. and no inflammatory cytokine responses after the WT CHIKV challenge, indicating that human CHIKV-specific neutralizing antibody titer around 150 $\mu PRNT_{50}$ in plasma of NHPs provided full protection against mild chikungunya disease induced by WT CHIKV in the animals.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

IXCHIQ

Chikungunya Vaccine, Live attenuated, Powder for Solution for Intramuscular Injection

Read this carefully before you receive **IXCHIQ**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **IXCHIQ**.

What is IXCHIQ used for?

- IXCHIQ is a vaccine for intramuscular injection for use in individuals 18 years of age and older to help protect against chikungunya virus (CHIKV).

How does IXCHIQ work?

IXCHIQ stimulates your immune system to make substances known as antibodies which fight the chikungunya virus. If a vaccinated person comes into contact with chikungunya virus their body can fight off the virus. Following a single intramuscular dose of IXCHIQ, it usually takes two to four weeks to be protected against chikungunya virus. As with all vaccines, 100% protection is not guaranteed.

What are the ingredients in IXCHIQ?

Medicinal ingredients: Purified live-attenuated chikungunya virus (CHIKV)

Non-medicinal ingredients: D-Sorbitol, L-Methionine, Magnesium Chloride, Potassium phosphate, Recombinant Human Albumin (rHA), Sucrose, Trisodium citrate di-hydrate.

IXCHIQ comes in the following dosage forms:

IXCHIQ, chikungunya vaccine, live, attenuated, is a lyophilized powder reconstituted with sterile water to form a sterile solution for intramuscular injection Each 0.5 mL dose of the vaccine contains not less than 3.0 log10 TCID50 of live attenuated chikungunya virus.

Do not use IXCHIQ if:

- you have an immunodeficiency (e.g., hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy) or if you are severely immunocompromised;
- you are allergic to any of the ingredients in the vaccine (see What are the ingredients in IXCHIQ?)
- you are pregnant. Women of child-bearing potential should be advised to avoid pregnancy for one month following vaccination.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take IXCHIQ. Talk about any health conditions or problems you may have, including if you:

- have had an allergic reaction to a component of IXCHIQ.
- have a bleeding disorder or a reduction in blood platelets, which increases risk of bleeding or bruising (thrombocytopenia) and cannot receive injections in the arm.

- have a weakened immune system, for example, due to a genetic defect, HIV infection, or certain medications such as cancer treatment.
- currently have any illness with a fever of more than 38.0 °C.
- take any medicines, even those you can buy over the counter.

Serious warnings and Precautions:

- As with all injectable vaccines, appropriate medical treatment and supervision should always be available to treat possible anaphylactic reactions following the administration of the vaccine.
- IXCHIQ must never be injected into a vein or any blood vessel.
- As with any other vaccine, vaccination with IXCHIQ may not result in protection in all people.
- Like other intramuscular injections, this vaccine should not be administered to persons with thrombocytopenia, hemophilia or other bleeding disorders.
- People with a medically-confirmed weak immune system (immunodeficiency) or taking medicines that can undermine the immune system (e.g., high-dose corticosteroids, drugs for rheumatoid arthritis or cancer drugs), IXCHIQ should not be given as it is a live vaccine.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with IXCHIQ:

- The Interactions with other drugs or other vaccines have not been established.

How to take IXCHIQ:

- IXCHIQ is given by a healthcare professional in a healthcare setting. It is given as an injection in the upper arm muscle in individuals 18 years of age and older.
- You should consult your health care provider on the duration of protection of IXCHIQ prior to potential re-exposure to CHIKV.
- You should still protect yourself from mosquito bites even if you have received the IXCHIQ vaccine.
- IXCHIQ does not protect against other diseases transmitted by mosquitoes.

Usual dose:

IXCHIQ is given as a single injection in the upper arm muscle.

Overdose:

There are no reported cases of overdose with IXCHIQ.

If you think you, or a person you are caring for, have taken too much IXCHIQ, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using IXCHIQ?

The most common side effects are headache, fatigue and muscle pain. Joint pain, fever, nausea, skin rash and vomiting may also occur. The most common injection site reaction is tenderness. Pain, redness, hardening, and swelling may also occur.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
• Difficulty breathing • Hoarseness or wheezing • Hives • Dizziness, weakness or fast heartbeat		X	X

These are not all the possible side effects you may have when taking IXCHIQ. If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Suspected Side Effects for Vaccines

For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional.

Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and Valneva cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php) and send it to your local Health Unit.

Storage:

Store in a refrigerator at 2°C to 8°C. DO NOT FREEZE. Do not use the vaccine after the expiration date shown on the vial label. Store in the original package.

After reconstitution, administer IXCHIQ immediately. If not used immediately, store the reconstituted vaccine at room temperature and administer within 30 minutes. DO NOT FREEZE RECONSTITUTED VACCINE.

Discard reconstituted vaccine, if not used within 30 minutes.

Keep out of reach and sight of children.

If you want more information about IXCHIQ:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.valneva.ca, or by calling Medical Information at Valneva Canada Inc. at 1-855-356-0831. Business hours: 9:00 a.m. to 5:00 p.m. Eastern Time, Monday to Friday.
- This leaflet was prepared by Valneva Austria GmbH.

Last Revised