Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

IXCHIQ powder and solvent for solution for injection
Chikungunya vaccine (live)

Chikungunya virus (CHIKV) Δ5nsP3 strain (live, attenuated)* not less than 3.0 log10 TCID50**

PLGB 43185/0007

Valneva Austria GmbH

LAY SUMMARY
IXCHIQ powder and solvent for solution for injection Chikungunya vaccine (live)

Chikungunya virus (CHIKV) Δ5nsP3 strain (live, attenuated)* not less than 3.0 log10 TCID50**

This is a summary of the Public Assessment Report (PAR) for IXCHIQ powder and solvent for solution for injection Chikungunya vaccine (live). It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as IXCHIQ in this lay summary for ease of reading.

This application was approved under International Recognition procedure (IRP). The Reference Regulator (RR) was the European Medicines Agency (EMA), with the procedure number (EMEA/H/C/0005797). The procedure followed route B.

This application was approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

For practical information about using IXCHIQ, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is IXCHIQ and what is it used for?
This application is a full-dossier application. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indications.
IXCHIQ is a vaccine that helps protect adults aged 18 years and older against disease caused by the Chikungunya virus (CHIKV).
Chikungunya is a disease that is caused by the chikungunya virus (CHIKV), which is found in the subtropical regions of the Americas, Africa, Southeast Asia, India, and the Pacific Region. CHIKV is spread to humans by the bite of an infected mosquito. The majority of people infected with CHIKV develop a sudden fever and severe pain in multiple joints. Other symptoms may include headache, muscle pain, joint swelling, or rash. These symptoms typically resolve within 7 to 10 days, but symptoms may last for months or years.

How does IXCHIQ work?
IXCHIQ works by teaching the immune system (the body's natural defence) to defend itself against CHIKV. The vaccine contains a form of the virus that has been weakened in the laboratory, so it cannot multiply. When the body encounters this weakened version of the virus, the immune system will recognise it and produce antibodies to attack it. When a person is given IXCHIQ, the immune system recognises the weakened virus as ‘foreign’ and produces antibodies against it. If the person later comes into contact with the chikungunya virus, the immune system will be able to fight off the virus more effectively and so help to protect the person against chikungunya.

How is IXCHIQ used?

The pharmaceutical form of this medicine is a powder and solvent for solution for injection and the route of administration is intramuscular (into the deltoid muscle within 2 hours of reconstitution).

The recommended dose is one injection into the muscle of the upper arm. The need for revaccination has not been established.

IXCHIQ has not been tested fully in children and adolescents aged 0 to 17 years. It should not be used in this age group.

For further information on how IXCHIQ is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This vaccine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner (HCP) if they have any questions concerning the vaccine.

What benefits of IXCHIQ have been shown in studies?

IXCHIQ is effective at triggering the production of antibodies against chikungunya virus, which is expected to reduce the risk of getting chikungunya.
The benefits of IXCHIQ were assessed in two main studies involving around 4,500 adults.
In one main study, over 4,000 people were given IXCHIQ or placebo (a dummy treatment). The study looked at whether IXCHIQ could trigger a level of antibodies expected to provide protection in about 400 of them. The target level of antibodies expected to provide protection was based on data from animal studies and information from people who were previously exposed to the chikungunya virus and who had developed immunity. One month after the injection, nearly 99% of people who received IXCHIQ had reached the target level of antibodies, compared with none of those who received a placebo. Follow-up data showed that two years after vaccination, this target level was maintained in 97% of people who received IXCHIQ.
Another main study involving around 360 people who all received IXCHIQ showed similar results, with 98% of people reaching the target level of antibodies one month after injection.
Based on these results, although no data were available on how well IXCHIQ protects people against the disease, the vaccine is expected to offer some protection.As part of the FDA's post-marketing requirements, two effectiveness studies will be conducted (one interventional and one non-interventional) including safety aspects (planned start in 2025).

What are the possible side effects of IXCHIQ?

For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By

reporting side effects, patients can help provide more information on the safety of this medicine.

The most common side effects with IXCHIQ (which may affect more than 1 in 10 people) include leucopenia, neutropenia and lymphopenia (low levels of white blood cells, including neutrophils and lymphocytes, as seen in blood tests), headache, fatigue, myalgia (muscle pain), joint pain (arthralgia), elevated liver enzymes as seen in blood tests, fever, nausea (feeling sick), and tenderness, pain, erythema (redness), induration (hardening) or swelling at the site of injection.
IXCHIQ must not be given to people who are immunodeficient or immunosuppressed (people with a weakened immune system) due to a disease or a treatment, such as people who are being treated with chemotherapy for a cancer, have an inherited immune deficiency, are taking a long-term immunosuppressive treatment (a treatment which reduces the activity of the immune system) or people with HIV who have a severely weakened immune system.

Why was IXCHIQ approved?
MHRA decided that the benefits are greater than the risks and recommended that this vaccine can be approved for use.
At the time of approval, there was no vaccine available to protect against chikungunya. Therefore, IXCHIQ was addressing an unmet medical need.

What measures are being taken to ensure the safe and effective use of IXCHIQ?
As for all newly-authorised vaccines and medicines, a Risk Management Plan (RMP) has been developed for IXCHIQ. The RMP details the important risks of IXCHIQ, how these risks can be minimised, any uncertainties about IXCHIQ (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for IXCHIQ:

Important Identified Risks	Chikungunya-like adverse reactions
Important Potential Risks	Vaccine-associated arthritis (swelling and tenderness of one or more joints after vaccination)
	Cardiac events
	Safety in pregnant or breastfeeding women
Missing Information	Safety in patients with autoimmune or inflammatory disorders
	Safety in frail patients with acute or progressive, unstable or uncontrolled clinical conditions, e.g. cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions
	Long-term safety data
	Co-administration with other vaccines

Additional pharmacovigilance activities are in place for IXCHIQ, such as carrying out further studies. The objectives of these studies are to elucidate and evaluate antibody persistence and long-term safety of live-attenuated chikungunya adult subjects, assess the safety and immunogenicity in moderately immunocompromised adults, describe the risk of adverse events of special interest, including laboratory-confirmed infection with chikungunya virus,

and evaluate pregnancy outcomes in the mother and infant who received IXCHIQ while pregnant.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of IXCHIQ are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about IXCHIQ
A marketing authorisation was granted in the United Kingdom on 04 February 2025.

The full PAR for IXCHIQ follows this summary.

This summary was last updated in March 2025.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare Products Regulatory Agency (MHRA) considered that the application for IXCHIQ powder and solvent for solution for injection, Chikungunya vaccine (live) (PLGB 43185/0007) could be approved.

The product is approved for the following indications:

- for active immunisation for the prevention of disease caused by chikungunya virus (CHIKV) in individuals 18 years and older.

The use of this vaccine should be in accordance with official recommendations.

The active substance is Chikungunya virus (CHIKV) Δ5nsP3 strain (live, attenuated)* not less than 3.0 log10 TCID50**, which belongs to the pharmacotherapeutic group of other viral vaccines.

Mechanism of action

IXCHIQ contains live-attenuated CHIKV of the ECSA/IOL genotype. The exact mechanism of protection against CHIKV infection and/or disease has not been determined. IXCHIQ elicits neutralising antibodies against CHIKV.

This application was approved under the International Recognition procedure (IRP). The Reference Regulator (RR) was the European Medicines Agency (EMA), with the procedure number (EMEA/H/C/0005797/0000).

This application was approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) (MHRA-100754-PIP01-22). The PIP was completed at the time of the application submission.

The licensing authority issued an opinion on compliance of the PIP (MHRA-100754-PIP01-22-M01-C1).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation was granted on 04 February 2025.

II. PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

The SmPC is in line with current guidelines and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

The PIL is in line with current guidelines and is satisfactory.

LABEL
The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS
MHRA considered that the quality of data submitted for this application is satisfactory.

The grant of a marketing authorisation was recommended.

IV. NON-CLINICAL ASPECTS
MHRA considered that the non-clinical data submitted for this application is satisfactory.

Ecotoxicity/environmental risk assessment
The vaccine is a live attenuated virus, and the product is presented in two parts, one a single dose vial with the virus present in a lyophilised form and the second part as a diluent in a syringe containing sterile water for injection intended to be used for reconstitution.

The intended posology is as a single intramuscular injection of 0.5 ml which contains at least 3.0 $\log_{10}$ $TCID_{50}$ (tissue culture infectious dose). Approval is sought for use in subjects aged 18 or older and the vaccine may be used in women who are pregnant.

The mode of action of this vaccine is not known: however, it does induce neutralising antibody responses specific to the virus that causes chikungunya disease. The virus is spread by mosquitoes and is an Alphavirus, with a positive-sense single stranded RNA genome. It causes a range of clinical manifestations, most notably, an acute and chronic arthritic reaction.
The virus in this vaccine has a 61-amino acid deletion in the replicase complex protein that attenuates its replication capacity, but the virus retains its capacity to elicit immune responses: these have been shown to be protective against a challenge with wild-type chikungunya in mice and monkeys.

The vaccine contains a genetically modified organism. The IRP is based on acceptance of the review by other regulatory agencies, in this case the EMA. The company supplied an environmental risk assessment (ERA). The conclusion on the safety of release into the environment of this virus is that in vaccinated subjects, the amount of virus present in the blood is not sufficient to result in infection of mosquitoes, with the inference that mosquitoes will not spread this genetically modified virus.

As per SI 2019No775, reg 50J2(a), and with reference to reg 58G(2), the company provided the consent of the Competent Authority for the deliberate release into the environment of the genetically modified organisms present in IXCHIQ.

The grant of a marketing authorisation was recommended.

V. CLINICAL ASPECTS
MHRA considered that the clinical data submitted for this application is satisfactory.

The grant of a marketing authorisation was recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, additional pharmacovigilance activities have been proposed (see table below for the risk minimisation measures and pharmacovigilance activities for all safety concerns):

Table 24: Important Identified Risk: Chikungunya-like adverse reactions

Evidence for linking the risk to the medicine	The following broad definition was used to identify Chikungunya-like adverse reactions in individuals who experienced at least one adverse event of special interest (AESI) in clinical trials with IXCHIQ: a) Fever (≥38 °Cor 37.8°C depending on the clinical trial) AND b) any single of the following symptoms: joint pain/arthritis (not only in extremities), an extreme sense of tiredness and lack of energy, chills, pain, peripheral oedema, headache, dizziness, paraesthesia (the feeling of tingling, numbness or "pins and needles"), muscle pain, back pain, rash, excessive sweating, eye disorders [e.g., conjunctivitis (inflammation of the outermost layer of the white part of the eye and the inner surface of the eyelid), inflammation of the retina, inflammation of the middle layer of tissue in the eye wall, swelling of the eye's optic nerve,…] and cardiac events [e.g., a heart rate of more than 100 beats per minute, abnormality of the heart's rhythm, myocarditis and other cardiac complications]) AND c) occurring within 30 days post vaccination (regardless of the order of their onset and duration). Adverse event combinations qualifying as Chikungunya-like adverse reactions were reported in 12.1% of participants. Among those, combinations of fever with headache, an extreme sense of tiredness and lack of energy, muscle pain or joint pain were the most common, all other symptoms were reported in fewer than 10% of Chikungunya-like adverse reactions. The reported symptoms were mostly mild. 1.8% of participants reported at least one severe symptom, most commonly fever or joint pain. Median onset of Chikungunya-like adverse reactions was 3 days after vaccination, and median time to resolution was 4 days. Longer-lasting symptoms ≥30 days occurred in 0.4% of participants." The vast majority of Chikungunya-like adverse reactions were unspecific symptoms consistent with a strong innate immune response, which are also seen after vaccination with other licensed, highly immunogenic vaccines and do not appear to reflect chikungunya-associated events. Clinically, the hallmark of chikungunya infection is high-grade fever and severe joint pain, while the AESI analysis used a very broad definition that factually allows any individual with fever and (among others) one of the solicited systemic AEs of joint pain, muscle pain, headache, and an extreme sense of tiredness and lack of energy, to qualify. In a typical presentation of chikungunya, it would be expected to see about 40% of individuals with acute disease to progress to chronic symptoms. If the approx. 12% of individuals with Chikungunya-like adverse reactions really were representing chikungunya-associated disease, the resulting rate of chronic disease would be a hypothetical 4%. This has, however, not been observed with VLA1553 at all: the overall rate of longer-lasting joint pain was not different between VLA1553 and placebo.
Risk factors and risk groups	Unknown.

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 "Special warnings and precautions for use" and section 4.8. "Undesirable effects" / PL section 4. "Possible side effects". Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Prospective Safety Cohort Study VLA1553-406. Post-Authorisation Safety Study VLA1553-401.

Table 25: Important Potential Risk: Vaccine-associated arthritis

Evidence for linking the risk to the medicine

In the Pooled Dataset (VLA1553-101, VLA1553-301, VLA1553-302), the proportion of subjects who experienced musculoskeletal stiffness, joint stiffness, joint swelling, arthritis, or osteoarthritis was comparable between the VLA1553 and placebo group (1.1% and 1.2%). All events were reported with low frequency (≤0.5% in the VLA1553 group).

Frequency of selected PTs per treatment group for the pooled dataset

	Statistic	**VLA1553 (N=3610)**	**Placebo (N=1033)**	**Overall (N=4643)**
Any Selected PTs	n (%) Obs [95% CI]	41 (1.1) 48 [0.8, 1.5]	12 (1.2) 12 [0.7, 2.0]	53 (1.1) 60 [0.9, 1.5]
Musculoskeletal and connective tissue disorders	n (%) Obs [95% CI]	41 (1.1) 48 [0.8, 1.5]	12 (1.2) 12 [0.7, 2.0]	53 (1.1) 60 [0.9, 1.5]
Musculoskeletal stiffness	n (%) Obs [95% CI]	17 (0.5) 20 [0.3, 0.8]	5 (0.5) 5 [0.2, 1.1]	22 (0.5) 25 [0.3, 0.7]
Osteoarthritis	n (%) Obs [95% CI]	11 (0.3) 11 [0.2, 0.5]	2 (0.2) 2 [0.1, 0.7]	13 (0.3) 13 [0.2, 0.5]
Joint stiffness	n (%) Obs [95% CI]	9 (0.2) 10 [0.1, 0.5]	2 (0.2) 2 [0.1, 0.7]	11 (0.2) 12 [0.1, 0.4]
Joint swelling	n (%) Obs [95% CI]	5 (0.1) 5 [0.1, 0.3]	2 (0.2) 2 [0.1, 0.7]	7 (0.2) 7 [0.1, 0.3]

	Arthritis n (%) Obs [95% CI] 2 (0.1) 2 [0.0, 0.2] 1 (0.1) 1 [0.0, 0.5] 3 (0.1) 3 [0.0, 0.2] Note. n = number of participants experiencing an event; Obs = number of events. All events of arthritis and osteoarthritis were assessed as not related to study vaccination by the investigator. In the pivotal clinical trial VLA1553-301, 16.7% of subjects reported solicited joint pain in the IXCHIQ arm, and 4.8% in the placebo arm. Of the cases reported in the IXCHIQ arm, 13.8% of cases were mild, 2.6% were moderate, and 0.3% of cases were severe. Of the total number of solicited cases of joint pain, 15.2% were considered related by the investigator in the IXCHIQ group compared to 4.5% in the placebo group. In the IXCHIQ group, most solicited systemic AEs occurred at a lower frequency in the elderly study population. Mild joint pain was reported in 14.3% of subjects aged 18 to 64 years compared to 10.1% of subjects ages ≥65 years. The most frequently observed AESIs were a combination of fever and joint pain.
Risk factors and risk groups	Unknown.
Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Prospective Safety Cohort Study VLA1553-406. Post-Authorisation Safety Study VLA1553-401.

Table 26: Important Potential Risk: Cardiac events

Evidence for linking the risk to the medicine	Cardiac events have been observed as rare events following vaccination such as influenza vaccination, COVID-19 vaccination, or smallpox vaccination (43). A limited number of cardiac events have been reported in IXCHIQ clinical trials. There were 5 participants in the IXCHIQ group for whom the following serious adverse events were reported: atrial fibrillation (2 individuals), cardiac arrest (1), cardiomyopathy (1), coronary artery disease (1). These serious events were assessed as not related to vaccination by the investigator. There is currently limited clinical evidence to attribute the possibility of a causal relationship between the occurrence of serious cardiac disorders and IXCHIQ vaccination. In addition, occurrence of cardiac events is rather frequent in the general population.
Risk factors and risk groups	E.g., age, positive family history, tobacco use, obesity.
Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Post-Authorisation Safety Study VLA1553-401. Prospective Safety Cohort Study VLA1553-406.

Table 27: Important Potential Risk: Safety in pregnant or breastfeeding women

Evidence for linking the risk to the medicine	Live vaccines tend not to be administered during pregnancy as a precaution because of the theoretical risk of foetal infection. There has been no evidence to date of direct foetal injury after the administration of live viral vaccines to pregnant women (42). Animal studies with IXCHIQ did not indicate direct or indirect harmful effects with respect to reproductive toxicity. Pregnant and lactating women were excluded from clinical trials with IXCHIQ so far. Nevertheless, 16 pregnancies were reported in individuals vaccinated with IXCHIQ. One participant was lost to follow-up. For 15 participants who were vaccinated with IXCHIQ during pregnancy outcomes were reported as follows: - live births with no congenital anomalies (10/15), spontaneous abortions (5/15, thereof one foetal death, i.e. foetus with Turner syndrome, 45 X genetic disorder). None of these outcomes were assessed as related to the vaccine by the investigator. An independent Data Safety Monitoring Board conducted a detailed review of all available data on the reported miscarriages and did not identify any safety concerns. The observed rate of spontaneous abortion (31.3%) is higher than those which typically occurs in the general population (about 12-16%); or in women vaccinated with mRNA COVID-19 vaccine (14.1%). However, these data should be interpretated with caution due to the small sample size compared to the general population.

	It is unknown if IXCHIQ is excreted in human milk. A risk to the breastfed child cannot be excluded. 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.
Risk factors and risk groups	Risk of exposure to wild-type CHIKV, gestational age, risks to the foetus or neonate from vertical transmission of wild-type CHIKV.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 "Fertility, pregnancy and lactation" / PL section 2. "What you need to know before you receive IXCHIQ". Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Post-Authorisation Pregnancy Study VLA1553-403. Post-Authorisation Pregnancy Study VLA1553-405.

Table 28: Missing Information: Safety in patients with autoimmune or inflammatory disorders

Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Post-Authorisation Safety Study VLA1553-401. Prospective Safety Cohort Study VLA1553-406. Clinical Trial VLA1553-304.

Table 29: Missing Information: safety in frail patients with acute or progressive, unstable or uncontrolled clinical conditions, e.g. cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions

Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Post-Authorisation Safety Study VLA1553-401. Prospective Safety Cohort Study VLA1553-406.

Table 30: Missing Information: Long-term safety

Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Clinical Trial VLA1553-303.

Table 31: Missing Information: Co-administration with other vaccines

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.5 "Interaction with other medicinal products and other forms of interaction" / PL section 2. "What you need to know before you receive IXCHIQ". Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Post-Authorisation Safety Study VLA1553-401. Prospective Safety Cohort Study VLA1553-406.

This is acceptable.

VII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The benefit/risk balance is, therefore, considered to be positive.
The quality of the product is acceptable. The submitted non-clinical and clinical data have shown the positive benefit/risk of this product for active immunisation in the prevention of disease caused by the chikungunya virus (CHIKV) in individuals 18 years and older.

The Summaries of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for these products are available on the MHRA website.

IX. TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPCs and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**