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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Invented name: Ixchiq

INN: Chikungunya vaccine (live)

Procedure number: EMA/REF/0000269473

Note:

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AEFI	adverse event following immunization
CDC	Centers for Disease Control and Prevention
CHIKV	chikungunya virus
CI	confidence interval
CISA	Clinical Immunization Safety Assessment
EC	European Commission
ETF	Emergency Task Force
EU	European Union
FDA	Food and Drug Administration
GMP	good manufacturing practice
ICSRs	individual case safety reports
LLT	lowest level term
MAH	marketing authorisation holder
MedDRA	medical dictionary for regulatory activities
PCR	polymerase chain reaction
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
RT-PCR	real-time PCR
SAE	serious adverse event
SmPC	summary of product characteristics
UMC	Uppsala Monitoring Centre
USA	United States of America
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization

1. Information on the procedure

As of 30 April 2025, 15 cases of serious adverse events (SAEs) following vaccination with Ixchiq have been reported by the marketing authorisation holder (MAH) both within and outside the European Union (EU). This included 9 cases from the EU (8 from France including La Réunion) and 6 from the United States of America (USA). Of the 9 serious cases reported from the EU, 4 have occurred in people older than 80 years of age with multiple underlying comorbidities and who required hospitalisation. Two (2) of these cases involved severe neurological complications in 84-year-old individuals, which in 1 case led to death whilst the other patient was recovering in hospital.

On 05 May 2025, the European Commission (EC) triggered a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data, and requested the Pharmacovigilance Risk Assessment Committee (PRAC) to assess the impact of the above concerns on the benefit-risk balance of Ixchiq and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

In addition, the EC requested the Agency to give its opinion, as to whether temporary measures were necessary to protect public health.

2. Scientific discussion

2.1. Introduction

Chikungunya disease is caused by infection with chikungunya virus (CHIKV), an alphavirus transmitted to humans by the bites of infected female mosquitoes (*Aedes aegypti* and *Aedes albopictus*). Symptoms of the acute phase of infection, lasting 7–10 days, include fever, arthralgia, myalgia, and rash. Severe manifestations are observed in subgroups of patients. Patients at extremes of the age spectrum are at higher risk for severe disease and risk factors for more severe chikungunya disease include intrapartum exposure for neonates, older age (> 65 years old), co-morbidities and co-infections. Many individuals also experience a chronic phase of the disease, primarily involving arthralgia (Suhrbier, 2019; Rama, 2024). The case fatality rate observed in different settings varies greatly, from ~0.038% in the 2025 outbreak in La Réunion (interim data)[1] to 0.35% in the 2015-2018 outbreak in Brazil (Mendonça, 2023). Higher rates are observed at age extremities and in males (Pérez-Estigarribla ,2025). Additionally, excess mortality has been reported in concomitance with large CHIKV outbreaks (Freitas, 2017; Freitas, 2024).

Ixchiq is a live attenuated chikungunya vaccine. It contains the live attenuated CHIKV Δ5nsP3 strain of the ECSA/IOL genotype. The exact mechanism of protection against CHIKV infection and/or disease has not been determined. However, Ixchiq elicits neutralising antibodies against CHIKV that have a major role in protecting against CHIKV infection and/or disease.

Ixchiq was granted an EU marketing authorisation on 28 June 2024 for the active immunisation for the prevention of disease caused by CHIKV in individuals 18 years of age and older, with extension to adolescents 12 years and older on 28 March 2025. The ability of the vaccine to prevent disease due to CHIKV was inferred from immunogenicity results of three clinical trials (VLA1553-301, VLA1553-302 and VLA1553-32) using a serological surrogate endpoint and demonstrating that a single dose induces robust CHIKV-specific neutralizing antibody responses. Notably, the clinical efficacy and effectiveness of the vaccination with Ixchiq remains to be quantified.

[1] estimated from https://www.ecdc.europa.eu/sites/default/files/documents/communicable-disease-threats-report-week-23-2025.pdf.pdf

According to the MAH, as of 13 May 2025, an estimated 37,917 doses have been administered across La Réunion, mainland France (including overseas departments), other EU countries, the United States, and Canada. Among these, the MAH estimated that 43% (16,236 doses) were administered to individuals aged 65 years and older.

Since January 2025, a large chikungunya outbreak has been affecting the EU French overseas departments, prompting a vaccination campaign targeting individuals over 65 years with comorbidities at risk of severe disease. The campaign was later expanded to include all individuals aged 18 and older. As of 25 April 2025, more than 44,000 confirmed cases of chikungunya disease had been reported from the French overseas territories of La Réunion, including at least 9 fatal cases[2].

On 28 April 2025, the MAH reported 2 serious cases following vaccination with Ixchiq via an emerging safety issue to EMA. On 29 April 2025, a signal procedure on adverse events (AEs) requiring hospitalisation in elderly patients was initiated.

As of 30 April 2025, 15 cases of SAEs following vaccination with Ixchiq had been reported by the MAH both within and outside the EU. Of the 9 serious cases reported from the EU, 4 occurred in people older than 80 years with multiple underlying comorbidities and who required hospitalisation. Two (2) of these cases involved severe neurological complications in 84-year-old individuals, which in 1 case led to death whilst the other patient was recovering in hospital. In both individuals, the vaccine strain of the chikungunya virus was detected in bodily fluids by polymerase chain reaction (PCR) method. As a consequence, the French public health authority (*Haute Autorité de Santé*) recommended a temporary suspension of vaccination with Ixchiq for individuals 65 years of age and older until the necessary investigations were completed[3]. In the USA, the 6 cases reported comprised neurological or cardiac SAEs following vaccination in travellers 67 years of age and older (source: Vaccine Adverse Event Reporting System [VAERS])[4]. Five (5) of these individuals were hospitalised and all recovered. All 6 patients had existing comorbidities. Although causality could not be determined by the MAH, association of vaccination with the SAEs was assessed as plausible by at least one Clinical Immunization Safety Assessment (CISA) expert. For this reason, at their meeting on 16 April, the Advisory Committee on Immunization Practices (ACIP) of the United States (US) Centers for Disease Control and Prevention (CDC) recommended precaution when vaccinating people older than 65 years depending on the risk of exposure[5]. Later in May, the US Food and Drug Administration (FDA) and the CDC jointly issued a safety communication recommending a pause in the use of the vaccine for individuals aged 60 years and older[6].

On 05 May 2025, the EC triggered a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of Ixchiq and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked. In addition, the EC requested the Agency/PRAC to give its opinion, as soon as possible, as to whether temporary measures are necessary to ensure the safe and effective use of this medicinal product.

[2] Available at: https://www.santepubliquefrance.fr/regions/ocean-indien/documents/bulletin-regional/2025/chikungunya-a-la-reunion.-bulletin-du-30-avril-2025
[3] Available at: Health authorities remove people aged 65 and over from the targets of the vaccination campaign against chikungunya with the Ixchiq vaccine in Reunion Island and Mayotte - Ministry of Labour, Health, Solidarity and Families
[4] Available at: Chikungunya Vaccine Information for Healthcare Providers | Chikungunya Virus | CDC
[5] Available at: ACIP CHIKUNGUNYA VACCINES WORK GROUP ; ACIP Meeting Information | ACIP | CDC
[6] Available at: https://www.fda.gov/safety/medical-product-safety-information/fda-and-cdc-recommend-pause-use-ixchiq-chikungunya-vaccine-live-individuals-60-years-age-and-older

On 07 May 2025, the PRAC recommended as temporary measure that Ixchiq should be contraindicated in individuals aged 65 years and older while the review was ongoing, and a thorough assessment of all available data performed[7].

The PRAC considered all available data, including the data provided by the MAH as well as the EudraVigilance analysis of all case reports in association with Ixchiq. A summary of the most relevant information is included below.

2.2. Data on safety

2.2.1. Clinical safety data

No new safety data from clinical trials have become available in the context of this procedure. Safety data supporting the use of Ixchiq in adults and adolescents were presented in the marketing authorisation application (EMEA/H/C/005797/0000) and in the context of a request for an extension of indication to individuals from 12 years of age (EMEA/H/C/005797/II/0001).

At the time the marketing authorisation was granted, the overall safety of Ixchiq was evaluated in 3,610 adult participants of three completed clinical studies including 346 subjects aged 65 years and older. These were studies VLA1553-301 (placebo-controlled Phase 3 US study – lyophilised formulation – targeted dose), VLA1553-302 (lot-to-lot consistency Phase 3 US study – lyophilised formulation – targeted dose), and VLA1553-101 (dose-response Phase 1 US study – liquid formulation – 3 different doses), with a total of 3,082, 408 and 120 subjects vaccinated and a median age of 45, 34 and 33 years, respectively (EPAR, EMEA/H/C/005797/0000).

The most common side effects with Ixchiq reported in the above studies were headache, nausea, myalgia, arthralgia, fatigue, fever, vaccination site reactions (tenderness, pain, erythema, induration, swelling), white blood cell count decrease and liver function test increase.

The occurrence of certain adverse event combinations, referred to as chikungunya-like adverse reactions, was retrospectively evaluated in the pooled safety dataset. Chikungunya-like adverse reactions were broadly defined as occurrence of fever (≥ 38°C) and at least one other symptom also reported for acute-stage chikungunya illness, including arthralgia or arthritis, myalgia, headache, back pain, rash, lymphadenopathy, and certain neurological, cardiac or ocular symptoms; within 30 days after vaccination, regardless of time of onset, severity or duration of the individual symptoms. Chikungunya-like adverse reactions were reported in 12.1% of participants. Among those, combinations of fever with headache, fatigue, myalgia, or arthralgia 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 arthralgia. 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.

Two participants had SAEs considered to be related to vaccination (versus none in the placebo arm): 1 case of myalgia and 1 case of syndrome of inappropriate antidiuretic hormone secretion/hypovolaemic hyponatraemia (and with severe atrial fibrillation assessed as unlikely related to vaccine). Death was reported in 2 vaccinated participants (severe coronary artery disease 119 days after vaccination, and severe COVID-19 165 days after vaccination) and were assessed as not related to vaccination.

When comparing the safety by broad age groups, solicited local and systemic AEs were less frequent in participants ≥ 65 years of age compared to participants 18-64 years of age. The frequency of

[7] Available at: IXCHIQ - Art 20PhV - PRAC assessment report

unsolicited (all, related and severe) AEs was comparable in each category. Serious AEs and medically attended AEs were more frequent in participants ≥ 65 years of age (3.5% and 17.6%, respectively) compared to participants 18-64 years old (1.2% and 11.8%, respectively). The rate of Chikungunya-like adverse reactions was comparable between the younger adults (18-64 years of age) (12.2%) and subjects ≥ 65 years of age (10.7%).

2.2.2. Post-marketing safety data

Between 09 November 2024 and 16 May 2025, the MAH received a total of 107 individual case safety reports (ICSRs), including 25 serious (23.4%) and 82 non-serious ICSRs (76.6%). Concurrently, for the purpose of this review, an extract from the EudraVigilance database was retrieved, with a later data cut-off date of 25 May 2025. The figures presented below are based on this extract.

As of 25 May 2025, 74 ICSRs of which 30 serious and 44 non-serious were reported. One (1) serious case was nullified since no exposure to Ixchiq was reported. Additionally, a duplicate was identified in the reported serious cases, reducing the number of serious cases to 28.

Of the 28 serious cases, 1 was reported from Austria, 1 from Canada, 8 from the USA, and 18 from France. Only 3 cases from France were recorded as involving travellers. For the remaining French cases, it was unclear of which part of France they originated from, e.g. mainland France or La Réunion.

Using the WHO-Adverse Event Following Immunization (AEFI) criteria, causality of the serious events with the vaccine was assessed as consistent in 6 cases (21%), as indeterminate in 15 cases (54%), as inconsistent in 1 case (4%), and as unclassifiable in 5 cases (18%). In the remaining case, which reported a syncope right after vaccination, the WHO-AEFI algorithm was not applied; anxiety-related reactions are known to occur with vaccination and section 4.4 of the Summary of Product Characteristics (SmPC) for Ixchiq adequately reflects this. The assessment using the WHO-Uppsala Monitoring Centre (UMC) criteria concluded in causality between the event and the vaccine to be probable for 7 cases (25%), possible for 19 cases (68%), unlikely for one case (4%), and unclassifiable for the remaining case (4%).

Of the serious events, 3 were fatal, 15 required hospitalisation and 10 were classified as serious based on other important medical events. The majority of patients were described to be recovering (11%) or having recovered (43%). All cases reporting a fatal outcome involved elderly males (age range: 77-88 years) with multiple underlying chronic conditions. The first case concerned an 84-year-old male who died from viral encephalitis and acute renal failure. Positive PCR and sequencing confirmed the vaccine strain in both blood and cerebrospinal fluid (CSF). Causality was assessed as "IV A – consistent" using the WHO-AEFI algorithm, and as "probable" using WHO-UMC criteria. The second case concerned an 88-year-old male who was already hospitalised at time of vaccination. His general condition deteriorated post-vaccination, and he died six days after vaccination due to aspiration pneumonia. The third case was reported in a 77-year-old male with Parkinson's disease whose general condition worsened two days after vaccination and who was hospitalised on day seven. The patient also died with aspiration pneumonia on day 14. Due to multiple confounders, the causality for both cases was assessed as "IV B – indeterminate" according to the WHO-AEFI system, and as "possible" using WHO-UMC criteria. Overall, a causal association between the events and Ixchiq could not be excluded.

A majority of patients presented symptoms associated with vaccine reactogenicity or adverse event combinations meeting the broad definition of chikungunya-like adverse reactions, reported in 15 cases (54%) and 13 cases (46%), respectively. The most frequently reported events in the serious cases, beyond those already listed in SmPC of Ixchiq, were: malaise with fall or syncope (n = 10; 36%); thrombocytopenia (n = 4; 14%); aggravation of cardiomyopathy, myocardial infarction, atrial flutter, or pericardial effusion (n = 4, 14%); general physical health deterioration or reduced general condition

(n = 4, 14%); decreased appetite, anorexia, appetite loss or hypophagia (n = 4, 14%); confusional state (n = 3, 11%); encephalopathy (n = 3, 11%); condition aggravated (n = 3, 11%); vision blurred or visual impairment (n = 3, 11%); acute kidney injury or serum creatinine increased (n = 4, 14%); encephalitis (n = 2, 7%; thereof one case reporting the Medical Dictionary for Regulatory Activities (MedDRA) lowest level term (LLT) encephalitis-like symptom). In addition, 1 case of aseptic meningitis was reported (traveller not exposed to wild-type virus).

Twenty-two (22) of out of 28 serious cases (79%) concerned individuals ≥ 65 years of age. The same proportion was reported in males. Additionally, 26 out of 28 serious cases (93%) had at least one comorbidity. Thereof, 21 cases concerned elderly (66-89 years of age) and 5 cases concerned adults 34-64 years of age. Out of the 26 individuals with comorbidities, 23 had multiple comorbidities. The most frequently reported comorbidities reflected common conditions such arterial hypertension (12 cases), dyslipidaemia (10 cases), and diabetes mellitus (7 cases). Additionally, there were 6 cases of coronary artery disease, 5 cases of hypothyroidism, and 5 cases of solid tumours, with 2 of these tumours being in remission. Chronic kidney disease and neurocognitive disorders were each reported in 4 cases, while chronic obstructive pulmonary disease or emphysema were noted in 3 cases. Most patients were poly medicated. For the 2 cases without co-morbidity reported, there was no hospitalisation reported (one case with vasovagal malaise and fall, and one with chikungunya-like adverse reactions).

A total of 6 serious cases involved individuals for whom conditions such as immunodeficiency or malignancy were specified in medical history. In these cases, the MAH categorised the administration of Ixchiq as off-label use. However, an immunocompromised state could only be confirmed for 3 cases, since for the other 3 cases, missing information (e.g., on concomitant medications or the status of the malignancy) did not allow to draw meaningful conclusions about the individual immune status.

Since the data cut-off date of the analysis presented above until 30 June 2025, 5 additional serious cases were retrieved from EudraVigilance. These cases concerned 3 elderly individuals (69-73 years of age) and two adults (28 and 62 years of age). Four cases involved males (80%). Reported events included: diarrhoea (n = 2); adrenocortical insufficiency acute; asthenia; bell's palsy; diplopia; lack of appetite; loss of consciousness; myalgia; myocardial infarction; pyrexia; vomiting (n = 1 each). For 3 cases, multiple underlying conditions were reported, 1 case concerned a healthy traveller and for 1 case no information on medical history was provided. Concomitant medication was reported for 3 cases (two poly-medicated) and co-vaccination also in 3 cases.

2.2.3. Discussion on safety data

The safety data reviewed originated from post-marketing sources. There were no new non-clinical safety aspects and no new data from clinical studies. No safety data regarding SAEs was identified through literature search.

A total of 73 cases, including 28 serious cases were retrieved from EudraVigilance as of 25 May 2025. Eighteen (18) of these cases (64%) were reported from France. Thirteen (13) cases (46%) concerned vaccinations administered in France in individuals not described as travellers and after the start of a national Ixchiq vaccination campaign in La Réunion island on 07 April 2025[8]. This increase in the number of safety reports highlights the vaccine's recent use beyond its previous use in travellers only.

The cases described chikungunya-like adverse reactions and severe reactogenicity with deterioration of general condition including malaise and decreased appetite, exacerbation of pre-existing diseases,

[8] French National Authority for Health released recommendation for IXCHIQ vaccination in La Reunion on 27 February 2025; launch of vaccine campaign on 7 April 2025.

confusional state, encephalopathy, or encephalitis, leading to falls, hospitalisation in 18 cases and death in 3 cases.

The majority of the serious cases reported concerned individuals ≥ 65 years of age (22 out of 28 cases; 79%). This finding might be explained by immunosenescence, the gradual weakening of the immune system due to aging, and concomitant conditions that impair or dysregulate immune responses. Notably, comorbidities tend to accentuate immunosenescence (Barbé-Tuana, 2020), and 93% of the cases had at least one underlying chronic condition (26 out of 28 cases). Still, the comorbidities identified among the cases were heterogeneous and reflected common pathologies (e.g. hypertension: n = 11; hyperlipidaemia/dyslipidaemia/hypercholesterolaemia: n = 8; diabetes mellitus: n = 7; coronary artery disease: n = 4; chronic obstructive pulmonary disease: n = 3). These comorbidities, as well as their associated medications, confounded the causality assessments. Moreover, the high prevalence of older adults with comorbidities among the cases may also be the result of a selection bias. Indeed, the majority of the reported cases originated from France where the recent Ixchiq vaccination campaign in La Réunion primarily addressed this vulnerable population at higher risk of severe CHIKV infection[9]. It is further noted that, in La Réunion, individuals 65 years and older received the majority of the vaccine doses, compared to individuals < 65 years of age. Similarly, if a higher proportion of males was observed among the serious cases (22/28, 79%), it remains unknown whether this relates to gender-differences in vaccine exposure, in prevalence of risk factors, or in capacity of the immune system to control the vaccine virus. Notably, among infants and older adults with chikungunya disease, higher case fatality rates have been reported in males (Pérez-Estigarribia, 2025).

Importantly, there has been limited vaccine exposure, particularly in < 65-year-olds in La Réunion as reported by France (approximately 500 doses, plus 1,200 healthcare professionals presumably younger than 65 and about 2,650 doses in ≥65 years). In the USA, if total doses in < 65-year-olds is estimated by the MAH at 14,675, persons with severe chronic conditions are likely underrepresented among the traveller population. Thus, it cannot be excluded that younger adults (< 65-year-olds) with underlying comorbidities also have a higher risk of SAEs with Ixchiq.

The assessment of post-marketing safety has proven to be challenging due to several uncertainties around the provided data. Firstly, as aforementioned, the reported adverse reactions were frequently confounded by co-morbidities and concomitant medications in multi-morbid patients and, among travellers, by co-vaccinations. Distinguishing between a new vaccine adverse reaction or a cascade of events triggered by the known reactogenicity could not always be established (e.g., fever and diarrhoea, leading to dehydration with prerenal failure as well as electrolyte disturbances, leading to encephalopathy). An additional uncertainty was the difficulty to differentiate vaccine virus from wild-type virus in chikungunya-like adverse reactions occurring in La Réunion. Although RT-PCR testing and sequencing methods were available on the island, these were not systematically performed in all cases. Also, the uncertainty around vaccine exposure numbers (distribution rather than administration numbers) and the absence of stratifications other than by age group (e.g., by gender, by indication [traveller/non traveller], by presence or absence of chronic conditions) prevented precise calculations and interpretation of SAE rates by risk group. Finally, the well-known limitations of passive pharmacovigilance surveillance (e.g., underreporting) are to be considered.

Despite these uncertainties, it is acknowledged that mostly elderly individuals with underlying chronic conditions were reported to have experienced serious adverse reactions after vaccination with Ixchiq.

[9] Risk groups targeted for Ixchiq vaccination according to French NITAG recommendations:
- Persons aged 65 years and older, particularly those with underlying medical condition (high blood pressure, diabetes, cardiovascular disease, respiratory disease, kidney disease, liver disease and neurovascular disease)
- Persons aged 18 to 64 years with underlying medical condition
- Professionals working in vector control

Even if the comorbidities might differ between the individuals, they share a susceptibility for adverse reactions including but not limited to chikungunya-like adverse reactions which often led to a deterioration of the general condition or an exacerbation of underlying chronic diseases, frequently requiring hospitalisations. However, it was not possible to identify an obvious pattern of predisposing comorbidities or comedications. Additionally, although only a minority of the serious cases reported (n = 2, 7%) had no co-morbidities reported, it cannot be concluded that elderly individuals without significant chronic medical conditions or younger adults with chronic conditions associated with impaired or dysregulated immune response are not at increased risk of severe adverse reactions.

Based on the data reviewed, several safety issues should be closely monitored by the MAH. The serious cases received post-marketing frequently reported neurological events, including, but not limited to, encephalopathy, encephalitis, and aseptic meningitis. The medical history of some individuals described chronic kidney disease, and an acute deterioration in kidney function was recorded as an adverse reaction following vaccination with Ixchiq in 4 cases. In 4 cases thrombocytopenia was observed. In an additional case of thrombocytopenia and acute renal failure, thrombotic microangiopathy (MedDRA LLTs haemolytic uraemic syndrome and nephrotic syndrome) was diagnosed. Since all these events can – and in some of the reported cases did – result in complications and unfavourable outcomes, they should be carefully monitored. Additionally, the MAH classified 6 of the serious cases as off-label use. However, an immunocompromised state could only be confirmed for 3 of these cases by the assessors. Whether these and the remaining 3 cases which did not provide sufficient information about the immune status of the individual, involved an off-label use or a medication error, remains unclear. Therefore, in future, monitoring of off-label use and medication errors should include a description and discussion of vaccine administrations to immunocompromised persons (including conditions leading to contraindication).

2.3. Data on quality

The case reports received prompted considerations regarding vaccine batches and the attenuation of the vaccine, including insufficient attenuation and the possibility of reversion to a more virulent phenotype. According to the MAH, all vaccine doses used derived from batches manufactured in compliance with the good manufacturing practice (GMP) requirements of the local regulatory authority and with the specifications in the marketing authorisation of the importing country. The MAH reviewed the batch processing, packaging and analysis records and found them to be in compliance with GMP.

Further, at least for immunocompetent individuals, there was no indication of an insufficient attenuation. There was no increase of SAEs in healthy adults. Preclinical studies from marketing authorisation application showed less efficient replication of the attenuated virus than that of wild-type virus (ca 1log lower concentration) and reduced swelling after injection in the feet of in C57BL/6 mice. Viraemia in healthy adults from phase I dose finding studies was short lived (cleared by day 14) and peaked at day 3 (reaching geometric mean titres of 7.4×10^4, 8.9×10^4 and 2.3×10^5 genomes per mL for the low, medium, and high dose groups, respectively). In contrast, viral loads from 10^9 to 10^{12} genomes/ml have been reported after wild-type infection. Clinical studies in healthy adults and adolescents showed a favourable safety profile.

It is agreed that the 183-nucleotide deletion in the genetically engineered CHIKV(Δ5nsP3) creates a high genetic barrier for reversion to a more virulent geno- and phenotype through compensatory mutations. The virus strain showed genetic stability after *in vitro* passage.

Additionally, in a situation where a person is infected with the wild-type virus shortly before or after vaccination, recombination between wild-type virus and attenuated (vaccine) virus might occur.

However, no data have been provided so far demonstrating the presence of such recombinants or of concomitant wild-type virus in any of the serious cases.

Therefore, an association of the reported serious cases with quality problems overall or of specific batches is considered unlikely.

2.4. Data on efficacy

No data on efficacy or effectiveness have become available in context of this procedure. Before the marketing authorisation of Ixchiq, efficacy trials were not considered feasible due to the unpredictable and short-lived outbreaks. Therefore, a threshold of CHIKV-specific neutralising antibody µPRNT50 titre of ≥150 was selected as surrogate marker for protection. It was agreed that this threshold could be considered as reasonably likely to predict protection even though it does not correspond to an established immune correlate of protection. Even if the exact mechanisms of protection are unknown, neutralizing antibodies have a major role in protecting against CHIKV infection and/or disease.

Pivotal immunogenicity data supporting the use of IXCHIQ in adults were from trials VLA1553-301 and VLA1553-302. Trial VLA1553-301 included elderly ≥ 65 years of age among its study population. The primary endpoint of the study was met, with 98.9% (95% CI: 96.7-99.8) of the baseline CHIKV seronegative participants vaccinated with a single dose of IXCHIQ achieving the predefined CHIKV-specific neutralizing antibody titre threshold (µPRNT50 ≥150) at Day 29. Similar proportions of vaccinated participants above the defined threshold were estimated for subjects aged 18-64 years (98.6% [204/207], 95% confidence interval [CI]: 95.8-99.7) and for subjects aged ≥65 years (100% [59/59], 95% CI: 93.9-100.0). Proportion of participants achieving the threshold was still high up to 2 years post-vaccination (97.1%, 95% CI of 94.4-98.7). Again, no difference in proportion above the threshold was noted when results were stratified by age groups. Results of study VLA1553-302 and study VLA1553-321 are in line with those of VLA1553-301.

Uncertainties remain around how the threshold value of neutralising antibodies actually translates into protection against disease (including chronic chikungunya) and/or infection. Therefore, although immunogenicity results of the pivotal trial VLAA553-301, VLA1553-302 and VLA1553-321 were compelling, their clinical relevance has not been established. In procedure EMEA/H/C/005797/0000, it was concluded that the actual protection conferred by Ixchiq needs to be confirmed.

Two effectiveness studies are planned: a test-negative case-control effectiveness study is intended to be carried out in Brazil (VLA1553-402), and a randomised controlled trial is planned to be conducted across various countries and regions (study VLA1553-404). VLA1553-404 is imposed as a post-authorisation efficacy study (PAES, Annex II condition) to address issues related to efficacy. The studies have not started yet, protocols are still under preparation, and feasibility evaluations are still ongoing. Whether these studies will generate interpretable data in a timely manner is still unclear at this stage. Additionally, and according to the data provided by the French national competent authority *Agence Nationale de Sécurité du Médicament et des Produits de santé*, an observational study CHIK RE VAC is currently ongoing in La Réunion to assess vaccine effectiveness and the duration of immunity acquired with Ixchiq. It is a prospective phase 4 study comparing two groups: (a) people vaccinated against chikungunya, and (b) those who refused vaccination. However, study enrolment is currently limited due to the temporary suspension of vaccination in patients ≥ 65 years and older.

Regarding the potential impact of a chikungunya vaccine campaign, two studies were published in 2025. The first study (Pérez-Estigarribia, 2025) used epidemiological data from a large outbreak in Paraguay in 2022 and 2023. Vaccine efficacy was assumed to be 75%. It was further assumed that 40% of individuals 12 years and older (2.2 million doses) being vaccinated over a 3-month period would have prevented 34,200 (95% CI, 30,900–38,000) cases, representing 23% of all cases,

including 17,100 (95% CI, 15,500–19,000) cases with chronic sequelae and 73 (95% CI, 66–81) deaths. The second study (Ribeiro dos Santos, 2025) used global seroprevalence data and assumed a vaccine efficacy against disease of 70% and a 40% efficacy against infection. It indicated that vaccinating 50% of individuals over the age of 12 in regions and during periods of virus circulation could prevent 4,436 infections, 0.34 deaths, and 17 disability-adjusted life years per 100,000 doses administered. However, neither study addressed the vaccine impact specifically in older adults or elderly.

Within the procedure, the MAH provided an observed versus expected analysis and a modelling exercise to calculate the net health benefit of Ixchiq. Due to multiple issues with the data and the assumptions used, the results of this exercise could not be used for a proper and accurate quantitative benefit-risk assessment of Ixchiq.

3. Benefit-risk balance

The PRAC reviewed the emerging safety data for Ixchiq, which included post-marketing safety data. No new non-clinical or clinical safety data were identified. Additionally, no data on clinical efficacy or effectiveness have become available in context of the review.

The new post-marketing safety data indicate an increased risk of serious adverse reactions in elderly individuals (22 out of 28 serious cases [79%] reported in individuals ≥ 65 years of age) and in individuals with at least one underlying chronic and/or uncontrolled medical condition. In twenty-six (26) out of 28 cases (93%), the patients had co-morbidities. Two (2) cases had no medical history reported. Of the 26 cases with co-morbidities, 23 patients had multiple comorbidities, mostly chronic conditions such as hypertension, diabetes mellitus and cardiovascular disease. The PRAC was of the view that the higher risk of serious adverse reactions in older adults is likely a result of poorer immunological control of vaccine-virus replication due to immunosenescence (reduced function of the immune system at an advanced age) and/or other pre-existing immunocompromising conditions. Similar observations have been made with other live-attenuated vaccines. However, in terms of predisposing comorbidities or comedications reported, PRAC could not identify an obvious pattern that would put individuals at higher risk of experiencing adverse reactions following vaccination. In addition to age and medical history, a higher proportion of serious cases has been reported in males (22/28 [79%]). Whether this relates to gender-differences in vaccine exposure, in prevalence of risk factors, or in capacity of the immune system to control the vaccine virus remains unknown. Therefore, since the same risk factors can be present in females, no risk distinction could be concluded by PRAC.

The cases reviewed showed a pattern of chikungunya-like adverse reactions and severe reactogenicity with general health deterioration, falls, exacerbation of chronic medical conditions, cardiac events, and neurological events, which in 18 cases involved hospitalisation, and, in 3 cases, death. In the majority of the serious cases, the events were either considered related to Ixchiq, or a possible relationship could not be excluded. To note, the causality was assessed as probable for a fatal case of an 84-year-old male with viral encephalitis and acute renal failure after receiving Ixchiq. This case was considered well-documented since the PCR and sequencing validated the presence of the vaccine strain in both blood and CSF. Based on this case, and considering the broader context of live attenuated vaccines, which have been associated with rare yet biologically plausible neurotropic adverse events such as encephalitis or meningitis, the PRAC concluded that the inclusion of encephalitis in sections 4.4 and 4.8 of the SmPC for Ixchiq is warranted. This case of fatal encephalitis and an additional case of aseptic meningitis raised the question of an insufficient attenuation or reversion to virulence of the vaccine virus. However, the PRAC noted that the risk of reversion to virulence is considered low due to the nature of the attenuation method which has demonstrated genetic stability. Also, there was no indication that the observed cases could be associated with quality-related deficiencies or deviations.

Overall, there are some data uncertainties with the post-marketing safety assessment described above. Most SAEs occurred in patients with multiple comorbidities, complicating the differentiation between vaccine-related adverse reactions and those arising from other factors. Additionally, in La Réunion, differentiating between the vaccine virus and the wild-type virus in individuals reporting chikungunya-like events was overall difficult as not all cases included information on CHIKV strain-specific testing. There is also some uncertainty with the vaccine exposure estimates, and the lack of detailed stratification of these numbers hindered precise SAE rate calculations. Lastly, the limitations of passive pharmacovigilance, such as underreporting, further contribute to the uncertainty.

In addition to the limitations related with the post-marketing safety data, the benefit-risk assessment was complicated by the absence of clinical efficacy or effectiveness data for Ixchiq, which remains to be confirmed through the planned post-authorisation studies. In an upcoming periodic safety update report (PSUR), within a year, the MAH is requested to present a risk-benefit analysis, using a validated methodology, for different scenarios considering age and epidemiological settings (see section 4.1.3.1).

At start of the present review, the PRAC considered that, in view of the seriousness of the events observed and the limited safety data in the population 65 years of age and above, it was appropriate to temporarily limit the exposure to vaccination with Ixchiq in this age group. However, following a thorough review of the available data, the PRAC considered that this population should not be excluded from vaccination. Elderly individuals are at increased risk of serious or complicated chikungunya disease from wild-type CHIKV infection and therefore are more likely to benefit from vaccination. Additionally, the data suggest that the risk of serious adverse reactions varies with age and individual medical history, rather than being uniformly distributed across the elderly population. Therefore, the use of Ixchiq should be carefully evaluated by the healthcare professionals on an individual basis irrespective of the age. As the benefits of the vaccine outweigh the risks, the PRAC concluded that the temporary contraindication for individuals 65 years of age and older should be removed (SmPC sections 4.1 and 4.3).

Importantly, it cannot be excluded that serious adverse reactions can occur in younger adults with underlying comorbidities. Such cases were available in the post-marketing data. However, the data is considered to be limited. Thus, the safety in individuals 12-64 years old with clinical conditions associated with impaired or dysregulated immune responses should be monitored in the currently planned additional pharmacovigilance activities (post-authorisation safety study VLA1553-401 and prospective safety cohort study VLA1553-406). The same studies should be used to further characterise the safety of Ixchiq in individuals aged 65 and older with chronic conditions. With this aim, the MAH is required to submit feasibility assessment reports.

In light of the severe reactions observed and the limited information on the risk in younger adults with underlying chronic and/or uncontrolled medical conditions, the PRAC concluded that, for all individuals, Ixchiq should only be given when there is a significant risk of acquiring chikungunya infection, and after careful consideration of the potential risks and benefits. The product information should be updated accordingly (SmPC section 4.4). Further, the product information should include information on the serious reactions reported in elderly and in individuals with multiple chronic or uncontrolled conditions (SmPC sections 4.4 and 4.8). The following adverse reactions, with the respective frequencies, should be added to the product information: encephalopathy, encephalitis, aseptic meningitis, confusional state, syncope, thrombocytopenia, malaise, and decreased appetite (SmPC section 4.8). Lastly, since the PRAC also noted cases of Ixchiq use in individuals who are immunodeficient or immunosuppressed, it was recommended to clarify the wording of the contraindication in these individuals (SmPC section 4.3). Overall, these product information amendments are considered sufficient to inform the healthcare professionals to perform a careful

evaluation of anticipated benefits and potential risks before vaccination, taking into account the characteristics of the individual, including medical history, co-morbidities, co-medication, the risk of CHIKV infection and the risk of complications from chikungunya disease. As currently stated in SmPC section 4.1, the use of this vaccine should be in accordance with official recommendations. A direct healthcare professional communication (DHPC) is to be distributed.

In addition to the product information amendments, no additional risk minimisation measures are considered necessary. As part of routine pharmacovigilance activities, the MAH should include detailed assessments of events of thrombotic microangiopathy, neurotropic adverse events, renal impairment, and thrombocytopenia in the upcoming PSURs, addressing causality, temporal relationship, and potential underlying risk factors. Additionally, the MAH should discuss vaccine administrations to immunocompromised individuals.

In view of the above, the Committee considers that the benefit-risk balance of Ixchiq remains favourable subject to the agreed amendments to the product information.

4. Summary of new activities and measures

4.1. Risk management

The MAH should operate a risk management system described in a Risk Management Plan which has been endorsed as part of this procedure.

4.1.1. Safety concerns

The Committee considered that "Increased risk for serious adverse events in individuals ≥ 65 years of age with chronic medical conditions" should be added as an important identified risk. Additionally, the Committee considered that "Safety in individuals 12-64 years old with clinical conditions associated with impaired or dysregulated immune responses, e.g. cancer, diabetes, cardiovascular disease, autoimmune diseases, haematological diseases, chronic liver disease, chronic kidney disease" should be added as missing information.

4.1.2. Risk minimisation measures

Amendments to the product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information would be necessary to minimise the risks associated with the use of Ixchiq. These changes include amendments to sections 4.1, 4.3, 4.4, and 4.8 of the SmPC.

The PRAC considered that the temporary contraindication in individuals aged 65 years and older should be lifted. As a consequence, this contraindication should be removed from section 4.3 of the SmPC and the indication in section 4.1 should be updated to reflect the use of Ixchiq in individuals aged 12 years and older, without a restriction in elderly.

Further warnings and precautions of use relating to the risks associated with the use of Ixchiq and the new adverse reaction 'Encephalitis' should be included in section 4.4. and section 4.8.

The PRAC also recommended to clarify the wording on the contraindication in individuals who are immunodeficient or immunosuppressed in section 4.3 of the SmPC.

Additionally, section 4.8 of the SmPC should be updated to reflect the following adverse reactions:

- Syncope, thrombocytopenia, malaise, and decreased appetite (frequency "Uncommon")
- Confusional state (frequency "Rare").
- Encephalopathy, encephalitis, and aseptic meningitis (frequency "Not known").

Administrative additions to section 4.4, in line with the recent QRD template, were introduced.

The Package Leaflet should be amended accordingly.

4.1.3. Pharmacovigilance activities

4.1.3.1. Routine pharmacovigilance activities

In the upcoming PSURs, the MAH is requested to:

- Discuss the following safety issues, including a detailed assessment of causality, temporal relationship, and potential underlying risk factors:
    - Thrombotic microangiopathy,
    - Neurotropic adverse events, including encephalopathy, encephalitis, aseptic meningitis, and other central nervous system manifestations,
    - Renal impairment including acute kidney injury, and
    - Thrombocytopenia.
- Include a description and discussion of vaccine administrations to immunocompromised persons (including conditions leading to contraindication) when reporting off-label use and medication errors.
- Provide separate vaccine exposure estimates and SAEs incidence rates for travellers and residents of endemic areas, stratified by age and gender when available.

In addition, the MAH should provide a new modelling exercise in an upcoming PSUR, within a year, with adequate assumptions and sensitivity analyses. The model should be stratified by age groups (12-17 years; 18-64 years; ≥ 65 years and older) and repeated for five different epidemiological settings (individuals living in low incidence outbreak areas, individuals living in high incidence outbreak areas, individuals living 10 years in endemic areas, travellers to endemic areas and travellers to high-risk outbreak areas). A risk-benefit analysis should be provided following a validated methodology, providing baseline, worst-, and best-case scenarios for all explored epidemiological situations (age groups; epidemiological context).

4.1.3.2. Additional pharmacovigilance activities

The safety concerns described in section 4.1.1. should be further characterised in the post-authorisation safety study VLA1553-401 and in the prospective safety cohort study VLA1553-406. For each study, a feasibility assessment report should be submitted by 31 December 2025.

4.2. Direct Healthcare Professional Communications and Communication plan

The Committee adopted the wording of a DHPC to inform the healthcare professionals of the serious adverse reactions reported with Ixchiq, the associated risk minimisation measures, and the lifting of the temporary contraindication in adults 65 years and older. The Committee also agreed on a communication plan.

5. Grounds for Recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Ixchiq.
- The PRAC reviewed all available data. This included data provided by the marketing authorisation holder, as well as the adverse reactions in EudraVigilance reported following use of Ixchiq.
- The PRAC identified several cases of concern, including three fatal cases. The PRAC noted that the majority of the serious cases concerned individuals aged 65 years and older and individuals with multiple underlying chronic and/or uncontrolled medical conditions.
- The PRAC was of the view that a higher risk of serious adverse reactions in older adults may be related to poorer vaccine-virus replication control due to immunosenescence (reduced function of the immune system at an advanced age) and pre-existing immunocompromising conditions.
- The PRAC considered that elderly individuals are more likely to benefit from vaccination since this population is at increased risk of hospitalisation and of death due to severe chikungunya infection. Therefore, as the benefits of the vaccine outweigh the risks, the PRAC concluded that the temporary contraindication for individuals 65 years of age and older should be lifted.
- The PRAC considered that information on the risk of serious adverse reactions in younger adults (below 65) with underlying medical conditions is currently limited.
- In light of the severe reactions observed and the limited information on the risk in younger adults with multiple underlying chronic and/or uncontrolled medical conditions, the PRAC concluded that, for all individuals, Ixchiq should only be given when there is a significant risk of acquiring chikungunya infection, and after careful consideration of the potential risks and benefits.
- The PRAC also noted cases of Ixchiq use in individuals who are immunodeficient or immunosuppressed and recommended that the wording of the contraindication in these individuals is clarified.
- In addition, the PRAC was of the view that the product information of Ixchiq should reflect the current knowledge on the occurrence of these serious adverse reactions, including the occurrence of encephalitis.

In view of the above, the Committee considers that the benefit-risk balance of Ixchiq remains favourable subject to the agreed amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for Ixchiq.

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