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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC assessment report on temporary measures

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 with all information of a commercially confidential nature deleted.

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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, namely, La Réunion) and 6 from the United States of America (USA). Of the 9 SAEs reported from the EU, 4 have occurred in people older than 80 years of age with multiple underlying comorbidities and who required hospitalisation. Two of these cases involved severe neurological complications in 84 years old individuals, which in one case led to death whilst the other patient is recovering in hospital. As a consequence, the French public health authority (*Haute Autorité de Santé* [HAS]) recommended a temporary suspension of vaccinations for individuals over 65 years old until the necessary investigations are completed and called for a reassessment of the benefit-risk balance of Ixchiq in subjects aged 65 years and over. In the USA, the 6 cases reported comprised neurological or cardiac SAEs following vaccination in travellers older than 67 years were reported (Vaccine Adverse Event Reporting System [VAERS]). Five of these individuals were hospitalised and all have recovered. For all 6 vaccinees, comorbidities were recorded. An association of these SAEs with the administration of Ixchiq was assessed as plausible. For this reason, at their meeting on 16 April 2025, the Advisory Committee on Immunization Practices (ACIP) of the United States (US) Centers for Disease Control and Prevention (CDC) recommended precaution when vaccinating people 65 years of age and older depending on the risk of exposure.

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/PRAC to give its opinion, as to whether temporary measures were necessary to protect public health.

The current report relates only to temporary measures recommended by the PRAC based on the preliminary data available at this time. These temporary measures are without prejudice to the outcome of the ongoing review under Article 20 of Regulation (EC) No 726/2004.

2. Scientific discussion

2.1. Introduction

Ixchiq is a live attenuated chikungunya vaccine. It contains the live attenuated chikungunya virus (CHIKV) Δ5nsP3 strain 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 and triggers a protective immune response against chikungunya virus in adults and adolescents that is maintained for at least 2 years after vaccination.

Ixchiq was granted an EU marketing authorisation on 28 June 2024 and is indicated for active immunisation for the prevention of disease caused by chikungunya virus in individuals 12 years and older. The ability to prevent disease due to chikungunya virus was based on a serological surrogate endpoint. However, the effectiveness of the vaccination with Ixchiq cannot yet be quantified. For this purpose, the MAH is conducting a randomised, controlled trial with pragmatic elements to assess the effectiveness of Ixchiq vaccination in the prevention of symptomatic, laboratory confirmed chikungunya after a single vaccination with Ixchiq in adults in endemic areas.

According to the MAH, as of 30 April 2025, an estimated 43,400 doses have been administered in post-marketing setting. The vaccine has been supplied in Austria, Belgium, Canada, France, Germany, Luxembourg, the Netherlands, the Nordic countries, and the USA.

At the time of granting the marketing authorisation, 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 (EMEA/H/C/005797/0000[1]).

The most common side effects with Ixchiq 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. Similar to other live attenuated vaccines, Ixchiq is contraindicated for patients who are immunodeficient or immunosuppressed due to disease or treatment (e.g., from haematologic and solid tumours, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy or patients with HIV infection who are severely immunocompromised), as outlined in section 4.3 of the Summary of Product Characteristics (SmPC).

The occurrence of certain adverse event combinations, referred to as chikungunya-like adverse reactions, was retrospectively evaluated in the pooled safety data. 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. Adverse event combinations qualifying as 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. Based on these data, sections 4.4 and 4.8 of the SmPC inform that Ixchiq may cause severe or prolonged chikungunya-like adverse reactions. Additionally, chikungunya-like adverse reactions, which include encephalitis, are an important identified risk in the risk management plan (RMP) of Ixchiq. *'Safety in patients with autoimmune or inflammatory disorders'* and *'Safety in frail patients with acute or progressive, unstable or uncontrolled clinical conditions, e.g. cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions',* which encompasses the patient population with these adverse drug reactions, are also considered missing information in the RMP.

When comparing the safety by broad age groups in the pooled safety data, solicited local and systemic adverse events (AEs) were less frequent in participants ≥ 65 years of age compared to participants 18-64 years of age. The frequency of unsolicited (all, related and severe) AEs was comparable in each category. Serious adverse events 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).

[1] Available at: https://www.ema.europa.eu/en/documents/assessment-report/ixchiq-epar-public-assessment-report_en.pdf

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. In the EU mainland, there have been localised outbreaks in the past, however in 2025, no autochthonous cases of chikungunya disease have been reported. As of 25 April 2025, more than 44,000 confirmed cases of chikungunya disease have been reported from the French overseas department of La Réunion, including at least 9 fatal cases[2].

On 28 April 2025, the MAH reported two SAEs via an emerging safety issue (ESI) to EMA. On 29 April 2025, a signal procedure on AEs requiring hospitalization in elderly patients was initiated.

As of 30 April 2025, 15 cases of SAEs following vaccination with Ixchiq have been reported by the MAH both within and outside the EU. Of the 9 SAEs reported from the EU, 4 have occurred in people older than 80 years with multiple underlying comorbidities and who required hospitalisation. Two of these cases involved severe neurological complications in 84-year-old individuals, which in one case led to death whilst the other patient is recovering in hospital. In both individuals, the vaccine strain of the chikungunya virus was detected in bodily fluids by polymerase chain reaction (PCR). As consequence, French public health authority (HAS) recommended a temporary suspension of vaccinations for individuals over 65 until the necessary investigations are completed and called for a reassessment of the benefit/risk balance of Ixchiq in subjects aged 65 and over, given the current uncertainties about the safety of this vaccine in this population[3]. In the USA, the 6 cases reported comprised neurological or cardiac SAEs following vaccination in travellers older than 67 years were reported (VAERS)[4]. Five of these individuals were hospitalised and all have recovered. All 6 people had a number of existing comorbidities. Although causality could not be determined, association of vaccination with the SAEs was assessed as plausible. For this reason, at their meeting on 16 April, the ACIP of the CDC recommended precaution when vaccinating people older than 65 years depending on the risk of exposure[5].

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.

For their assessment on the need for any temporary measures, the PRAC considered all available data, including the data provided by the MAH, in writing and at an oral explanation, as well as the Eudravigilance analysis of all cases reports in association with Ixchiq conducted following the signal initiated on 29 April 2025. A summary of the most relevant information is included below.

2.2. Data on safety

An Eudravigilance analysis for all case reports in association with active substance high level CHIKUNGUNYA VIRUS, STRAIN CHIKV LR2006-OPY1, LIVE ATTENUATED was conducted. As of 02 May 2025, 52 cases were identified in total, thereof 20 serious, mainly reported in the USA and in France:

[2] Available at: https://www.santepubliquefrance.fr/recherche/#search=chikungunya
[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

- 8 cases reported from the USA (presented in Table 1) – 6 cases in elderly males (67-86 years,), 1 case not related to Ixchiq (72-year-old female did not receive the vaccine), and 1 case describing a syncope following vaccination (34-year-old male).
- 11 cases reported from France (thereof 9 from La Réunion) – 8 males (62-84 years), 3 females (76-89 years) (presented in Table 2) – 2 cases with fatal outcome (case 2 and 8). One case concerned an 84-year-old male who also developed encephalitis with PCR evidence of the vaccine strain in the cerebrospinal fluid. The second fatal case related to a 77-year-old male with Parkinson's disease whose deglutition worsened, probably resulting in aspiration pneumonia.
- 1 case reported from Austria – 1 case describing fatigue, myalgia, arthralgia, pyrexia and chills (48-year-old male). At time of reporting, the patient had not recovered from the symptoms described.

All individuals experienced reactions in temporal association with the vaccination, with the exception of 1 case in the USA involving a 72-year-old female who did not receive the vaccine.

The relevant serious cases reported in the USA involved vaccinees between 67 and 86 years of age (see Table 1). Only in 1 case, a chikungunya virus PCR was performed, which turned out to be positive. In another case, neutralising antibodies of the IgM class against chikungunya virus were detected in cerebrospinal fluid.

The patients' medical history mainly included common conditions such as hyperlipidaemia (n=4 individuals) and hypertension (n=4). However, coronary artery disease (n=3), chronic heart failure (n=2) and diabetes mellitus (n=1) were also reported. The body mass index could only be calculated for case 6 (24.6) and was within the normal range. The time between the vaccination and the onset of symptoms ranged from 3 to 5 days, which appears plausible when considering vaccination reactions.

Five of the cases described a febrile deterioration of the subject's condition, 3 with symptoms of encephalopathy. Atrial flutter and hypotension were recorded in 1 case each.

Table 1: Summary of the six relevant case characteristics reported in the USA

Case	Age (years)	Sex	Key comorbidities	Symptom onset (days)	Discharge diagnosis(es)	Chikungunya testing
1	83	Male	Coronary artery disease, chronic heart failure, chronic kidney disease, hypertension, hyperlipidaemia, chronic thrombocytopenia	3	Encephalopathy, generalised weakness	N/A
2	77	Male	Coronary artery disease, hypothyroidism, benign prostatic hyperplasia, hyperlipidaemia, hypertension, IgA deficiency	4	Acute metabolic encephalopathy, fever of unknown origin	N/A
3	86	Male	Diabetes mellitus, heart failure, anaemia, hypertension, hypothyroidism, hyperlipidaemia	3	Metabolic encephalopathy, fever possibly related to postvaccination inflammatory response	RT-PCR on serum on day 13: positive
4	68	Male	Prostate cancer, hypothyroidism, hypertension, dyslipidaemia	5	Aseptic meningitis	IgM & neutralising antibodies in cerebrospinal fluid

5	67	Male	Hyperlipidaemia	4	Atrial flutter, non-ST segment elevation myocardial infarction	N/A
6	74	Male	Ischemic cardiomyopathy, hypotension, coronary artery disease, chronic leukopenia, chronic thrombocytopenia	3	Worsened and prolonged hypotension on background of pre-existing cardiomyopathy and hypotension	N/A

Adapted from: https://www.cdc.gov/acip/downloads/slides-2025-04-15-16/04-Hills-chikungunya-508.pdf

The 11 serious cases reported from France affected individuals aged between 62 and 89 years (see Table 2). In 4 cases, PCR results for chikungunya virus are available and positive, and in 3 cases the vaccine strain was identified. The medical history of the individuals varied in terms of type and extent of conditions. In 2 cases, only a medical history of glaucoma and hypertension was described, respectively. However, 8 cases reported multiple chronic conditions, e.g. cardiac conditions such as myocardial infarction, stent placement or mitral valve repair (n=5), type 2 diabetes mellitus (n=3), or chronic obstructive pulmonary disease (n=2). For 1 case, no medical history was specified. Information on weight and height were available in 9 cases, allowing to calculate the body mass index. Elevated indices were only present in 2 cases (case 2, 30.9; case 4, 26.6). From the information available so far, the cases reported from La Réunion may be described as to involve more vulnerable subjects than the cases reported in the USA. This could be due to the chikungunya outbreak in this region and the resulting vaccination campaign, as opposed to the USA where Ixchiq is recommended for travellers.

For most cases (n=8), the time between the vaccination and the onset of the first symptoms ranged from 2 to 4 days. Three cases reported a time to onset of 5 to 8 days. Most reports describe a quite rapid deterioration of the general condition, often accompanied by chikungunya-like symptoms such as fever and arthralgia. One of the fatal cases involved an aggravation of Parkinson's disease with fluctuating swallowing disorder, probably leading to aspiration pneumonia and sepsis. In the other fatal case, acute oligo-anuric renal failure and encephalitis were diagnosed. Acute renal failure was also reported in some of the other serious cases. This might be associated with dehydration but needs to be evaluated during further investigations. Five individuals developed symptoms such as drowsiness and vertigo, sometimes resulting in falls or difficulty to get up or to stand. This alone did not lead to hospitalisation but was categorised as serious.

Table 2: Summary of the 11 case characteristics reported in FR (EudraVigilance)

Case	Age (years)	Sex	Medical history, concurrent conditions	Symptom onset (days)	Reactions (MedDRA preferred terms [PTs])	Chikungunya testing
1	84	Male	Arterial hypertension, insulin-requiring type 2 diabetes mellitus, gout, chronic renal failure	2	Arthralgia, asthenia, chikungunya test, decreased appetite, disorientation, encephalopathy, lymphopenia, pyrexia, thrombocytopenia, tremor	PCR (blood) positive for vaccine strain (day 10)
2 (fatal)	84	Male	Myocardial infarction (2005), type 2 diabetes mellitus, asthma, sleep apnoea syndrome	2	Acute kidney injury, asthenia, chikungunya test, encephalitis, fall, pyrexia	PCR (blood) positive for vaccine strain (day 8) PCR (CSF) positive for

						vaccine strain (day 9)
3	82	Male	Sciatica, benign prostatic hyperplasia, lumbar spinal stenosis (2023), hypogammaglobulinaemia, ankylosing spondylitis, sleep apnoea syndrome, vertigo positional, pulmonary embolism (2012), Factor II mutation, arthritis reactive	3	Chikungunya test, fall, malaise, pyrexia	PCR (blood) positive for vaccine strain (day 19)
4 (traveller)	64	Male	Thymoma (operated 2024), chronic obstructive pulmonary disease, pericarditis	3	Arthralgia, C-reactive protein increased, pyrexia	PCR (blood) positive for CHIK (blood, urine; day 11)
5	89	Female	Stent placement, lupus-like syndrome, hip arthroplasty	4	Hyponatraemia, myalgia, nausea, pyrexia, vision blurred, diarrhoea	No CHIK PCR performed
6	72	Male	Hypertension, chronic obstructive pulmonary disease, hypercholesterolaemia	6	Asthenia, headache, malaise, nausea, neck pain, vertigo	Not reported
7	67	Male	Not reported	3	Diarrhoea, fall, malaise, pyrexia	Not reported
8 (fatal)	77	Male	Hypertension, myocardial infarction, Parkinson's disease	2	Acute kidney injury, asthenia, pneumonia aspiration	No CHIK PCR performed
9	76	Female	Hypertension	5	Confusional state, nausea, vertigo	Not reported
10	62	Male	Marfan's syndrome, insulin-requiring type 2 diabetes mellitus, prostate cancer stage IV, mitral valve repair	4	Arthralgia, fall, fatigue, malaise, nausea	Not reported
11 (traveller)	80	Female	Glaucoma	8	Thrombocytopenia, haemolysis, nephrotic syndrome	No results yet

3. Benefit-risk balance

Out of the 20 cases identified in the Eudravigilance analysis of 02 May 2025, 1 case was excluded from further analysis since the individual did not receive the vaccine. The PRAC noted the 19 serious safety cases, including 2 fatal cases, reported globally following vaccination with Ixchiq as of 02 May 2025. Of particular significance are 17 serious cases involving 14 males and 3 females aged between 62 and 89 years. All cases describe a deterioration in condition, 11 with fever. Two cases were fatal. One of the 2 cases with fatal outcome involve an 84-year-old male who also developed encephalitis with PCR evidence of the vaccine strain in the cerebrospinal fluid. The second fatal case relates to a 77-year-old male with Parkinson's disease whose dysphagia worsened, probably resulting in aspiration pneumonia.

While most of the safety reports include details of previous and concomitant conditions, at this stage the PRAC could not identify a specific pattern of comorbidities or comedications which are probably associated with an increased risk of serious reactions following vaccination. It is however acknowledged that increased age and comorbidities may impact the immune responses to the vaccine.

Most of the serious cases observed concern individuals aged between 62 and 89 when vaccinated. The safety data available from clinical studies is limited in individuals 65 years and older. In the pivotal phase 3 trial, while overall AEs were less frequent in participants 65 years and older than in participants up to 64 years of age, more SAEs were recorded. However, the interpretation of the age subgroups is limited by the low number of participants in the clinical trials. Additionally, when looking at age strata for older participants, the clinical data is more limited, with only 54 participants (1.5%) aged 75-84 years and 5 participants (0.1%) over 85 years. In contrast, the data from clinical studies is considered more comprehensive for individuals below 65 years of age. In addition, it is noted that administration to individuals who are immunodeficient or immunosuppressed due to disease or medical therapy is already contraindicated regardless of the age, as for other live attenuated vaccines.

To address the safety concern raised by the post-marketing safety cases, the MAH proposed the introduction of a warning or precaution relating to frail individuals 75 years of age and older, especially those with comorbidities, under section 4.4 of the SmPC. However, it was considered that the inclusion of a statement relating to an "elderly frail" population is ambiguous and cannot be clearly defined. In addition, based on the cases reported, not all elderly individuals who experienced serious adverse reactions can be described as frail individuals. The MAH further proposed to define as contraindication the use in elderly population (65 years and above) especially with comorbidities potentially affecting immune response to the vaccine. Based on the available data, as described above, PRAC could not identify a specific pattern from the spectrum of pre-existing conditions reported in the case reports reviewed. The review of the cases did not allow to identify particular conditions as risk factors for serious adverse reactions following vaccination with Ixchiq. Therefore, the MAH proposals are not considered effective temporary measures that could help the healthcare professional identify individuals at higher risk and consistently implement these in clinical practice.

The PRAC noted that, according to the MAH, the currently available information limits the ability to properly assess the causality for the serious cases described. While it is acknowledged that elderly individuals are at increased risk of severe circulating wild-type chikungunya virus infection and serious or complicated chikungunya disease, the PRAC considers that, in view of the seriousness of the events observed and the limited safety database in the population 65 years of age and above, it is appropriate to temporarily limit the exposure to vaccination with Ixchiq in this age group until a thorough review of the data is completed. Therefore, the PRAC recommends, as a precaution, that Ixchiq should be contraindicated in individuals aged 65 years and older.

The above temporary measures should be reflected in the product information of Ixchiq and communicated to healthcare professionals via a dedicated letter. The adequacy of these temporary measures will be reviewed as part of the ongoing Article 20 procedure.

4. Summary of new activities and measures

4.1. Amendments to the product information as temporary measures

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

The indication was restricted to individuals between 12 and 64 years of age.

In addition, the PRAC considered that Ixchiq use should be contraindicated in individuals aged 65 years and older.

The package leaflet was amended accordingly.

4.2. Direct healthcare professional communication and communication plan

The Committee adopted the wording of a DHPC to communicate the temporary restrictions described above to healthcare professionals. 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, in particular regarding the need for temporary measures in accordance with Article 20(3) of Regulation (EC) No 726/2004 for Ixchiq.
- The PRAC reviewed the available data. This included data provided by the marketing authorisation holder, in writing and at an oral explanation, as well as the serious adverse events reported following use of Ixchiq in Eudravigilance.
- Among these events, the PRAC identified several cases of concern in individuals aged 65 years and older, including two fatal cases. The PRAC could not identify a pattern of comorbidities or comedications in the cases reviewed that could further identify the individuals at higher risk when exposed to the vaccine.
- The PRAC noted that the safety data from clinical studies in individuals aged 65 years and older is limited and considered that these emerging and serious post marketing adverse events may have an impact on the benefit-risk balance of Ixchiq in this population.
- The PRAC also noted that administration to individuals who are immunodeficient or immunosuppressed due to disease or medical therapy is already contraindicated regardless of the age.
- Therefore, PRAC temporarily recommends as a precaution that Ixchiq should be contraindicated in individuals aged 65 years and older while the review is ongoing, and a thorough assessment of all available data is performed.

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

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

This recommendation is without prejudice to the final conclusions of the ongoing procedure under Article 20 of Regulation (EC) No 726/2004.