Annex IV

Scientific conclusions

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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 chikungunya virus (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, 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.

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 European Union (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 serious AEs following vaccination with Ixchiq had been reported by the marketing authorisation holder (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 United States of America (USA), the 6 cases reported comprised neurological or cardiac serious AEs 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 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 soon as possible, as to whether temporary measures are necessary to ensure the safe and effective use of this medicinal product.

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.

Overall summary of the scientific evaluation by the PRAC

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 summary of product characteristics (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 serious AEs 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 serious AE 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.

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 professional 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.

Grounds for PRAC 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 Ixchiq could be given to individuals 65 years of age and older. As a consequence, 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.

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

The CHMP, as a consequence, considers that the benefit-risk balance of Ixchiq remains favourable subject to the amendments to the product information described above.

Therefore, the CHMP recommends the variation to the terms of the marketing authorisations for Ixchiq.