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Japanese Encephalitis Vaccine (Inactivated, Adsorbed) [IXIARO®]

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Contents

Abstract

▲ The Japanese encephalitis vaccine IC-51 (IXIARO®) is an inactivated virus (strain SA_{14}-14-2) that is manufactured in cultured Vero cells and is currently being developed for preventive vaccination against the Japanese encephalitis virus.

▲ Administration of IXIARO® as a two-dose treatment in healthy adults provided high levels of seroprotection against Japanese encephalitis virus. Immune responses at 56 days post-vaccination, including seroconversion rates and geometric mean titres, were noninferior to those seen with a currently available licensed vaccine. Seroprotection was achieved 1 week after second vaccination.

▲ Long-term seroprotection was also observed with the vaccine, with seroconversion rates and geometric mean titres maintained at both 6 and 12 months post-vaccination.

▲ Coadministration with a hepatitis A vaccine had no effect on the immunogenicity of IXIARO®. Additionally, the vaccine immunogenicity was not compromised in subjects with pre-existing vaccine-induced antibodies for tick-borne encephalitis, a related flavivirus.

▲ Vaccine immunogenicity was also observed in paediatric volunteers, with seroconversion rates not significantly different to an active comparator at 56 days post-vaccination.

▲ The safety and tolerability profile of IXIARO® was generally similar to that of placebo with respect to systemic adverse events, and was associated with a numerically lower frequency of local injection site adverse events than the active comparator vaccine.

Features and properties of Japanese encephalitis vaccine (inactivated, adsorbed) [IXIARO®]	
Indication	
For immunization against Japanese encephalitis virus in adults	
Vaccine composition	
Vaccine comprises formalin-inactivated Japanese encephalitis strain SA_{14}-14-2 adsorbed to an aluminium hydroxide (0.1%) adjuvant	
Dosage and administration (in clinical trials in healthy adult volunteers)	
Dose	Two doses of 6μg (in 0.5 mL)
Route of administration	Intramuscular injection into deltoid muscle
Frequency of administration	Vaccination at 0 and 28 days
Most common adverse events (>10%)	
Systemic	Headache, myalgia, influenza-like illness, fatigue
Injection site	Tenderness, pain

Japanese encephalitis is an acute viral infection of the CNS that causes an inflammation of the meninges and of the brain itself in humans. It is caused by a mosquito-borne flavivirus and is the most common cause of viral encephalitis in Asia, with at least 50 000 cases of clinical disease estimated to occur annually, with virtually all countries in Asia affected.[1,2] The incidence of clinical disease varies between countries, with annual incidences ranging from <10 to >100 per 100 000 people.[3] Of these cases, 25% are fatal and a further 30% of patients experience neuropsychiatric sequelae; children aged <10 years and the elderly are more susceptible.[2,4] There is currently no specific medication available to treat Japanese encephalitis virus infection.

The Japanese encephalitis virus is transmitted in an enzootic cycle between mosquitoes and vertebrate animals. Transmission occurs when a mosquito, most commonly *Culex tritaeniorhynchus*, becomes infected after biting a viraemic animal, primarily domestic pigs and wading birds.[5] The virus is subsequently passed on by the mosquito through biting another animal, with humans also susceptible, although humans are considered a 'dead end' host as they develop only low levels of viraemia and consequently do not transmit the virus.[5] Human infections are therefore likely to occur in rural areas where large numbers of mosquitoes breed in close proximity to livestock.[3]

Non-immune travellers who visit endemic areas are also at risk, although the extent of this depends on numerous factors, including the season of travel (transmission season), proximity to rural areas, duration of travel and activities undertaken (e.g. extended time outdoors).[2]

An inactivated mouse brain-derived vaccine (JE-VAX®) has been used as the principal vaccine against Japanese encephalitis and is licensed in the US, Canada, Israel and Australia for the vaccination of travellers and military personnel.[2,6] However, serious adverse events, including hypersensitivity reactions such as utricaria, angioedema and respiratory distress have restricted immunization recommendations for this vaccine.[2,6] Importantly, the onset of these events can be delayed by up to 2 weeks.[2,6] As such, vaccinees are advised to remain in reach of medical care for 10 days following injection.[1] Furthermore, this vaccine has been associated with a moderate frequency of injection site adverse reactions, such as tenderness, redness and swelling, as well as mild systemic adverse reactions including headache, myalgia, fever and nausea.[1]

The specific vaccine constituents responsible for these adverse events have not been specified, although the involvement of gelatin stabilizers appears likely.[7] Furthermore, because the vaccine originates from mouse brain, concerns have been raised regarding potential neurological adverse effects, whilst the presence of unidentified infectious agents is also possible.

Given these disadvantages, a new vaccine, Japanese encephalitis vaccine IC-51 (inactivated, adsorbed) [IXIARO®], has been developed to overcome some of these issues. IXIARO® is based on an inactivated Japanese encephalitis virus strain, namely SA_{14}-14-2, that is manufactured in cultured Vero cells, a technique currently being used in the development of rabies and polio vaccines. Vero cells support the growth of Japanese encephalitis viruses to a high titre in the absence of serum, with simple and efficient subsequent purification steps in comparison to the mouse brain-derived vaccine.[8] Furthermore, unlike the mouse brain-derived vaccine, IXIARO® does not contain gelatin or animal proteins, which should theoretically reduce the potential for hypersensitivity and neurological reactions.[8]

This article discusses the immunogenicity and tolerability of IXIARO® in healthy adult and paediatric volunteers. Medical literature referenced in this profile was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles.

1. Immunogenicity

The immunogenicity of IXIARO® has been evaluated in several randomized, single-[9] or observer-blind,[10-13] active comparator-controlled,

multicentre studies in healthy adults aged ≥18 years (one trial[9] only available in abstract form).

Studies in adults were phase III trials,[9,10,12,13] one of which was a pivotal noninferiority study.[12] The pivotal noninferiority study[12] included 867 healthy adults recruited from 11 sites in North America and Europe and compared the immunogenicity of IXIARO® with a US-licensed comparator vaccine (JE-VAX®). Additionally, the effect of pre-existing vaccine-induced immunity for tick-borne encephalitis on the immunogenicity of IXIARO® has been examined in 420 healthy volunteers from the pivotal immunogencity trial,[12] 54 of whom had received basic and/or booster vaccination against tick-borne encephalitis in the previous 10 years.[13]

In another phase III study, the effect of concomitant vaccination for hepatitis A (with HAVRIX®1440) on the immunogenicity of IXIARO® was evaluated in 192 volunteers.[9]

In one further randomized, blinded study in 374 volunteers, the effect of a rapid immunization schedule and immune response kinetics was also examined.[10]

The noncomparative, follow-up study involved 298 healthy adults who had participated in either the noninferiority trial[12] or a phase III safety and tolerability trial[14] that examined the long-term immunogenicity of the vaccine.[11]

The immunogenicity of IXIARO® has also been examined in healthy paediatric volunteers in a phase II, randomized, comparator-controlled, open-label, single-centre, dose-confirmation study in children ≥1 and <3 years of age (n = 60); the comparator in this trial was JenceVac®, a Japanese encephalitis vaccine produced using the inactivated Nakayama strain [data presented as abstracts].[15,16]

In three of the studies[9,12,13] and the follow-up study,[11] volunteers were vaccinated with 'ready-to-use' IXIARO® 6 μg in 0.5 mL of 0.1% aluminium hydroxide, administered intramuscularly into the deltoid muscle at days 0 and 28.

In the study assessing the effect of concomitant vaccine treatment,[9] volunteers received a further injection at day 0 of either placebo (0.5 mL) or hepatitis A vaccine HAVRIX®1440 (1.0 mL). In the rapid immunization study,[10] volunteers received either a standard (IXIARO® 6 μg at both 0 and 28 days) or a rapid immunization schedule (administered as either a single standard dose [6 μg] or a single high dose [12 μg as two doses of 6 μg] at day 0 only). In the paediatric dose-confirmation study,[15,16] children received either 6 μg (n = 24) or 3 μg (n = 24) of IXIARO® at days 0 and 28.

Where the comparator vaccine JE-VAX® was used,[11-13] 1 mL of the comparator vaccine was injected subcutaneously into the upper arm of volunteers at days 0, 7 and 28, according to recommended guidelines.[17] Study blinding was maintained by use of a placebo injection consisting of 0.1% aluminium hydroxide in phosphate-buffered saline.[11,12] Where another comparator vaccine (JenceVac®) was used,[15,16] the comparator vaccine was administered as a 0.5 mL subcutaneous injection on days 0, 7 and 28 (n = 12).

Common primary endpoints for IXIARO® immunogenicity were used across trials, which included seroconversion rates and geometric mean titres (GMTs) for anti-Japanese encephalitis virus neutralizing antibodies determined in serum samples obtained 56 days after the initial vaccination.[9,10,12,15,16] A coprimary immunogenicity endpoint in the study evaluating concomitant vaccination with IXIARO® and HAVRIX®1440 was GMTs for anti-hepatitis A virus antibodies at day 28.[9] In the long-term follow-up study, immunogenicity measurements in addition to the 56-day data were taken at 6 and 12 months following vaccination, although the latter timepoint was not controlled.[11] In paediatric volunteers, immunogenicity measurements were taken at both 28 and 56 days,[15,16] whilst for the rapid-dose study,[10] additional measurements were taken at days 10, 28 and 35.

Immunogenicity was determined by quantification of Japanese encephalitis virus-specific neutralizing antibodies using the plaque-reduction neutralization test (PRNT).[9-13,15,16] Seroconversion rates were determined as the percentage of volunteers with a >1 : 10 serum dilution resulting in a 50% plaque reduction ($PRNT_{50}$). The demonstration of neutralizing antibody titre of >1 : 10 has been agreed as a surrogate for efficacy

of Japanese encephalitis vaccines and is regarded as indicative of seroconversion.[18,19] GMT values were subsequently calculated from $PRNT_{50}$ values.

In the pivotal noninferiority study,[12] noninferiority of IXIARO® to the comparator vaccine was indicated if the lower limit of the 95% confidence intervals for seroconversion difference (IXIARO® minus the comparator) was greater than −10% and if the lower limit of the GMT ratio (IXIARO®/comparator) was greater than 1/1.5. In the rapid immunization study,[10] noninferiority of the seroconversion rate for the single high-dose vaccination regimen at day 56 was indicated if the lower limit of the 95% confidence interval for the between-group difference in seroconversion rate was greater than −10%. In the trial evaluating concomitant IXIARO® and HAVRIX®1440 vaccination versus IXIARO® alone, noninferiority of the concomitant vaccination was established if the lower bound of the 95% confidence interval for the GMT ratio was >0.5[9] for the comparison between IXIARO® plus HAVRIX®1440 and IXIARO® at day 56 and IXIARO® plus HAVRIX®1440 and HAVRIX®1440 at day 28. Where stated, analyses for efficacy endpoints were based on the per-protocol[10,12] or intention-to-treat populations.[9,11,13]

- In the pivotal noninferiority study,[12] IXIARO® was noninferior to the comparator vaccine in terms of seroconversion rates for neutralizing antibodies and GMTs. Seroconversion rates at 56 days post-vaccination were 98% in IXIARO® recipients compared with 95% in the comparator vaccine group (figure 1).[12] Corresponding GMTs were 244 for IXIARO® compared with 102 for the comparator vaccine, again demonstrating noninferiority of IXIARO® (figure 1).
- Furthermore, at 56 days the immunogenicity of IXIARO® was not affected in volunteers with pre-existing immunity for the tick-borne encephalitis virus.[13] Seroconversion rates in volunteers who tested positive for tick-borne encephalitis were 77% at 28 days following the initial IXIARO® 6 μg vaccination and were significantly higher compared with tick-borne encephalitis-negative volunteers (49%; $p < 0.0001$). However, after the second IXIARO® 6 μg vaccination at 56 days, no between-group differences were observed between tick-borne encephalitis-positive (96%) or -negative (91%) volunteers.[13]

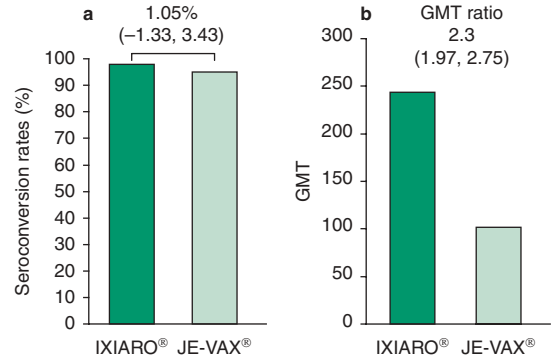

Fig. 1. Immunogenicity of IXIARO® in healthy adults. Data are presented for both (**a**) the seroconversion rates and (**b**) the geometric mean titres (GMTs) of antibodies against Japanese encephalitis virus 56 days after the first dose of either IXIARO® (n = 430) or comparator vaccine JE-VAX® (n = 437) in adults aged ≥18 years participating in a randomized, observer-blind, multicentre, noninferiority trial.[12] IXIARO® 6 μg was administered on days 0 and 28 and JE-VAX® 1 mL on days 0, 7 and 28. Noninferiority between vaccination groups was indicated if the lower limit of the 95% confidence interval (CI) for the seroconversion difference (IXIARO® minus JE-VAX®) was greater than −10% and GMT ratio estimate (IXIARO®/JE-VAX®) was >1/1.5. Risk difference estimate for seroconversion rates (calculated using Mantel-Haenszel risk difference estimator), ratio estimate for GMTs and CIs are shown above the bars; noninferiority of IXIARO® was demonstrated for both seroconversion rates and GMTs vs JE-VAX®.

- In the study evaluating the long-term immunogenicity of IXIARO®, seroprotection was sustained for up to 12 months.[11] Seroconversion rates at 56 days post-vaccination were 99% for IXIARO® recipients compared with 98% for the comparator vaccine (figure 2). Immunogenicity was maintained at the 6-month timepoint with seroconversion rates of 95% in IXIARO® recipients, which was significantly higher than that observed in the comparator group (74%) [figure 2]. Seroconversion rates in the placebo group were 14% at 56 days and 9% at 6 months. At 12 months, seroconversion rates in IXIARO® recipients remained at 83.4% (figure 2).[11]
- Corresponding GMT values were higher in IXIARO® recipients than with the comparator vaccine at both 56 days (311 vs 100, respectively) and at 6 months (84 vs 34) [figure 2].[11] GMT values for the placebo group were 9 at 56 days

and 6 at 6 months. At the 12-month timepoint, GMT values had declined to 41 in IXIARO® recipients (figure 2), although this was well within the protective margins of >1 : 10.[11]

- Concomitant vaccination for hepatitis A had no effect on the immunogenicity of IXIARO®.[9] The noninferiority of the concomitant vaccination schedule was established as the lower bound of the 95% confidence interval for the GMT ratio at day 56 was 0.7541. No between-group differences in GMT levels at 56 days were observed in volunteers who received either IXIARO® alone (n = 192) or concomitant IXIARO® and HAVRIX®1440 vaccination (n = 203).[9] Notably, GMT values for hepatitis A virus did not differ with or without concomitant IXIARO® vaccination and noninferiority of concomitant vaccination was seen (lower bound of 95% confidence interval for GMT ratio at 28 days was 0.8115).[9]
- The standard two-dose IXIARO® vaccination protocol is the preferred regimen, based on results of the rapid immunization schedule trial.[10] Noninferiority of the single high-dose regimen, relative to the standard regimen, was not shown at day 56 (seroconversion rates of 41% vs 97%; between group difference −56% [95% CI −65.6, −46.6]). In volunteers receiving the standard vaccination protocol, seroconversion rates after the first dose were 21% and 40% at days 10 and 28, compared with 54% and 66% in single high-dose (12 μg) recipients and 29% and 43% in the single standard-dose (6 μg) recipients.[10] In volunteers receiving the second dose in the standard vaccination protocol group, seroconversion rates increased to 97% at days 35 and were maintained at day 56, while rates had fallen at these timepoints in both single high-dose (59% and 41%) and single standard-dose (38% and 26%) recipients.[10]
- Additionally, GMT values in volunteers treated with the standard vaccination protocol reached 8, 11, 266 and 218 at days 10, 28, 35 and 56 compared with those treated with the single high-dose (17, 23, 18 and 11) or single standard-dose (9, 11, 13 and 8) vaccination protocols.[10]
- In the dose-finding study in paediatric volunteers, no between-group differences in seroconversion rates were observed at 56 days following vaccination with IXIARO® 3 μg (96%), IXIARO® 6 μg (95%) or the active comparator JenceVac® (91%). Additionally, no significant differences in seroconversion rates were seen at 28 days (65%, 71% and 64%, respectively).[15] Similarly, no significant differences were seen in GMT values at either 56 (24, 21 and 20, respectively) or 28 days (201, 218 and 230, respectively).[16]

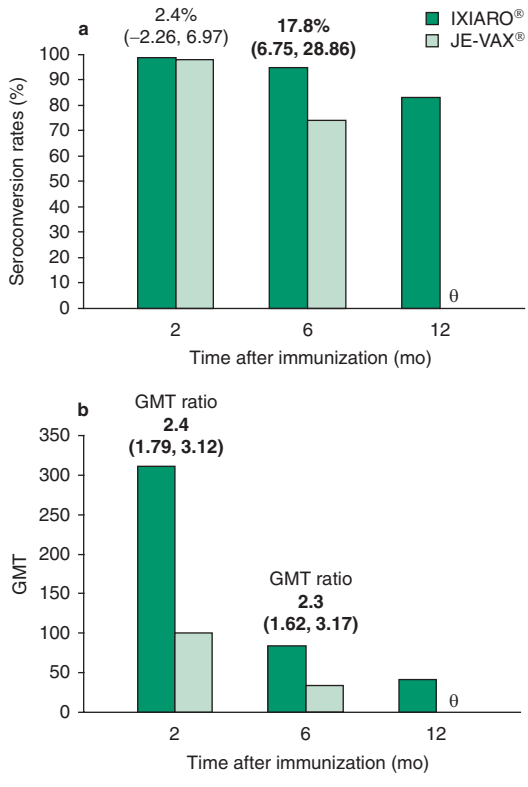

Fig. 2. Long term immunogenicity of IXIARO® in healthy adults. Data are presented for both (**a**) the seroconversion rates and (**b**) the geometric mean titres (GMTs) of antibodies against Japanese encephalitis virus at 56 days (2 months), 6months and 12months after the first dose of IXIARO® (n = 181) or 56 days (2 months) and 6 months after the first dose of comparator vaccine JE-VAX® (n = 82) in adults aged ≥18 years participating in a randomized, observer-blind, multicentre, follow-up study.[11] IXIARO® 6 μg was administered on days 0 and 28, and JE-VAX® on days 0, 7 and 28. Patients were drawn from the pivotal immunogenicity phase III trial[12] and a phase III safety and tolerability trial.[14] Risk difference estimate for seroconversion rates (calculated using Mantel-Haenszel risk difference estimate), ratio estimate for GMTs and 95% confidence intervals are shown above the bars; values in bold indicate significant differences between groups. θ indicates data were not collected.

2. Tolerability

Data concerning the safety and tolerability of IXIARO® were obtained from a randomized, double-blind, placebo-controlled, multicentre study in 2650 healthy adults aged ≥18 years who received IXIARO® 6 μg (at least one dose) or placebo (0.1% aluminium hydroxide in phosphate-buffered saline), administered at days 0 and 28.[14] These data were supplemented with tolerability data from the studies described in section 1 in both healthy adult[10-12] and paediatric volunteers.[15]

Across most studies, injection site adverse events were recorded daily in a diary maintained for 7 days following each injection.[10-12,14] Systemic adverse events were also recorded throughout the duration of each study.[10-12,14] In the pivotal safety and tolerability study,[14] serious adverse events and medically attended adverse events (primary endpoints) were recorded from the time of the first vaccination up to 4 weeks after the second vaccination.

A further pooled analysis in volunteers (n = 4715) who were vaccinated with IXIARO®, JE-VAX®, HAVRIX® or placebo provided an overview of the long-term tolerability of IXIARO® up to 6 months post-vaccination.[20] Data were from five phase III efficacy trials, as well as two safety follow-up studies; 3558 volunteers received IXARO®.[20] This analysis is available in abstract form only.

- IXIARO® was generally well tolerated across studies, with an adverse event profile generally similar to that of the comparator vaccine and placebo.[11,12,14] The most common injection site adverse events and systemic adverse events following immunization occurring in IXIARO® and placebo recipients in the large randomized, safety and tolerability trial[14] are summarized in figure 3. Common adverse events at the vaccination site in IXIARO® and placebo recipients were tenderness, pain, redness and hardening, while the most common systemic adverse events were headache, myalgia, influenza-like illness and fatigue (figure 3).[14]
- The rates of serious adverse events following immunization were 0.5% in IXIARO® recipients compared with 0.9% for placebo, although none were considered to be related to the vaccination.[14] The most common medically attended general adverse events with IXIARO® or placebo were influenza-like illness (1% vs 0.9%) and headache (0.9% vs 1.1%).[14]
- The tolerability profile of IXIARO® in the rapid immunization study was consistent with that of the safety and tolerability study,[14] and the incidence of local and systemic adverse events did not differ between the high-dose and standard-dose vaccination groups.[10]
- In an active-comparator trial, the tolerability profile of IXIARO® was generally similar to that of the comparator vaccine JE-VAX®, although the incidence of some severe injection site adverse events was significantly lower with IXIARO® ($p < 0.0001$).[12] For instance, injection site redness occurred in 1% of IXIARO® recipients versus 11% of JE-VAX® recipients, while swelling (0.7% vs 5.3%) and hardening (1.0% vs 5.2%) were also less frequently reported with IXIARO®.[12]
- The systemic adverse event profile did not differ significantly between IXIARO® and JE-VAX® recipients, with the most common adverse events after immunization being headache (26% and 29% for IXIARO® and JE-VAX®), myalgia (21% and 16%), influenza-like illness (13% and 13%) and fatigue (13% and 11%).[12]
- The most common adverse events occurring 8 weeks to 6 months after the first vaccination in the follow-up study were nasopharyngitis (3.4%, 4.7% and 4.9% for the Japanese encephalitis IXIARO®, JE-VAX® and placebo, respectively), influenza-like illness (1.1%, 1.5%, 0.6%) and headache (1.8%, 0.3%, 1.1%).[11] At 12months, nasopharyngitis (3.9%), cystitis (2.8%) and headache (2.8%) were the most frequently reported adverse events with IXIARO® treatment.[11]
- In the pooled long-term tolerability study,[20] systemic adverse reactions over the 6-month study period following injection were reported in 40% of IXIARO® recipients compared with 40% and 36% for placebo and comparator vaccine recipients, respectively. Additionally, injection site adverse events were reported in

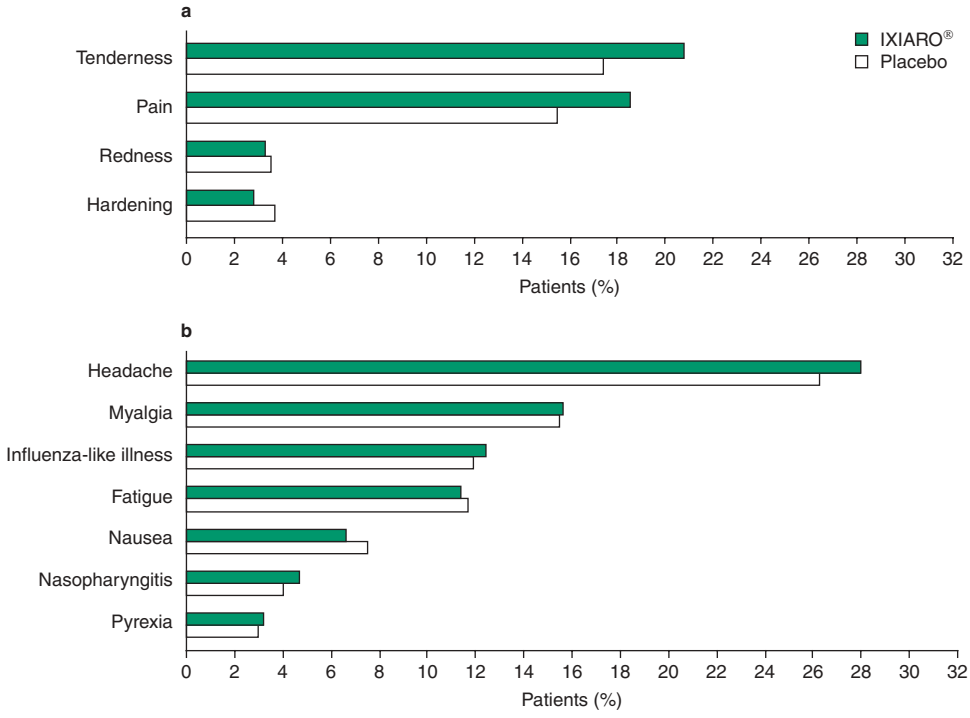

Fig. 3. Tolerability profile of IXIARO® in healthy adults. Incidences of (**a**) injection site and (**b**) systemic adverse events following immunization regardless of cause occurring at a rate of ≥3%, in a randomized, double-blind, placebo-controlled, multicentre study in healthy adults aged ≥18 years[14] who received IXIARO® 6 μg (n = 1993) or placebo (n = 657) intramuscularly at days 0 and 28. Injection site adverse events recorded 1 day after the first vaccination, and systemic adverse events across the total study period (0–56 days) are shown.

54% of IXIARO® recipients, compared with 56% and 61% for placebo and comparator vaccine recipients.[20]

- In paediatric volunteers, no between-group differences were seen in the number of volunteers experiencing at least one adverse event with IXIARO® 3 μg (12.5%), IXIARO® 6 μg (20.8%) or the comparator vaccine JenceVac® (33.3%).[15]

3. Dosage and Administration

The dose of IXIARO® used across trials was 6 μg in 0.5 mL for the initial vaccination, followed by a further 6 μg at 28 days. When available, local prescribing information should be consulted for information on contraindications, precautions, potential drug interactions and use in special patient populations.

4. Japanese Encephalitis Vaccine (Inactivated, Adsorbed) (IXIARO®): Current Status

The Japanese encephalitis vaccine IXIARO® is approved in Australia and is currently awaiting marketing approval in the US, EU, Canada and Switzerland. It has received a positive opinion from the Committee for Medicinal Products for Human Use of the European Medicines Agency.[21] The vaccine is likely to be indicated for active immunization against Japanese encephalitis virus for adults that are at risk of exposure to the virus.

IXIARO® demonstrated considerable seroprotection (seroconversion rates and GMTs) in clinical trials and was noninferior to the licensed comparator vaccine JE-VAX® at 56 days. Long-term seroprotection up to 12 months was also demonstrated with IXIARO® vaccination.

Additionally, the immunogenicity of IXIARO® was not decreased in volunteers with pre-existing immunity for tick-borne encephalitis or in volunteers concomitantly vaccinated for hepatitis A.

IXIARO® is generally well tolerated with a better injection site adverse event profile than the currently licensed comparator vaccine.

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