HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

23 September 2009

IXIARO suspension for injection
Pack of 1 prefilled syringe + 1 needle (CIP: 393 958-0)
Pack of 1 prefilled syringe (CIP: 393 959-7)

Applicant: NOVARTIS VACCINES

Inactivated Japanese encephalitis virus, strain SA14-14-2 inactivated produced in Vero cells

ATC (2009): J07BA02

List I

Orphan medicinal product status

Date of centralised MA: March 31, 2009

Reason for request: inclusion on the list of medicines approved for use by hospitals.

The High Council for Public Health recommends that the Japanese encephalitis vaccine be made available only in international vaccination centres.

Enclosed:
- Opinion of the High Council for Public Health of April 24, 2009 regarding recommendations for vaccination against Japanese encephalitis;
- Health recommendations for travellers in 2009 (BEH Nos. 23-24)

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Japanese encephalitis virus, strain SA14-14-2 inactivated produced in Vero cells

1.2. Background

The first vaccine to be granted an MA in the prevention of Japanese encephalitis.

1.3. Indication

"IXIARO is indicated for active immunization against Japanese encephalitis in adults.

IXIARO should be considered for use in individuals at risk of exposure through travel or in the cause of their occupation".

1.4. Dosage

"Adults

The primary vaccination series consists of two separate doses of 0.5 ml each, according to the following schedule:
First dose: day 0.
Second dose: 28 days after the first dose.
The duration of protective immunization is not known. The schedule and the impact of booster immunization are currently being investigated.

It is recommended that vaccinees who received the first dose of IXIARO complete the primary 2-dose vaccination course of IXIARO.

Children

IXIARO is not recommended for children and adolescents due to the lack of date on safety and efficacy data.

Method of administration

The vaccine should be administered by intramuscular injection into the deltoid muscle. It should never be injected intravascularly.
Exceptionally, IXIARO can also be administered subcutaneously to patients with thrombocytopenia or bleeding disorders since bleeding may occur following an intramuscular administration. Subcutaneous administration could lead to a suboptimal response to the vaccine (see section 4.4 of SPC). It should be noted, however, that there are no clinical efficacy data to support administration by subcutaneous route".

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

J : General anti-infectives for systemic use
J07 : Vaccines
J07B : Viral vaccines
J07BA : Encephalitis vaccines
J07BA02 : Encephalitis, Japanese, inactivated, whole virus

2.2. Medicines in the same therapeutic category

No vaccines in the same therapeutic category benefit from an MA.

Two vaccines have been made available through nominative provisional licences: JE-VAX then JAPANESE ENCEPHALITIS VACCINE.

2.3. Medicines with a similar therapeutic aim

None

3 ANALYSIS OF AVAILABLE DATA

The immunogenicity and safety of IXIARO have been analysed in 4 phase III studies on 3,709 patients over the age of 18:

- study IC51-301 aiming to demonstrate the non-inferiority of IXIARO compared to JE-VAX in terms of immunogenicity
- study IC51-302 evaluating the safety of IXIARO compared to placebo
- follow-up study IC51-303: extension of studies IC51-301 and IC51-302 to 24 months evaluating the immunogenicity of IXIARO (in progress)
- study IC51-308 aiming to demonstrate the non-inferiority of the IXIARO+HAVRIX combination compared to IXIARO alone and HAVRIX alone in terms of immunogenicity.

3.1. Immunogenicity

3.1.1. Study IC51-301[1]

The primary endpoint of this randomised single-blind study on 867 subjects over the age of 18 was to demonstrate the non-inferiority of the immunogenicity of the IXIARO vaccine (2 injections) compared to the JE-VAX vaccine (3 injections) available through nominative provisional licences until 2008 and which is no longer marketed.

Vaccination schedule:

- IXIARO 6 µg group: two IM injections of 0.5 ml on day 0 and day 28 and one placebo injection on day 7 (n=430);

[1] Tauber E, Kollaritsch H et al. Safety and immunogenicity of a Vero-cell-derived, inactivated Japanese encephalitis vaccine: a non inferiority, phase III, randomised controlled trial. The Lancet. 2007; 370:1847-53

- JE-VAX group: three SC injections of 1 ml on day 0, 7 and 28 (n=437).

Primary endpoints (PP population):
- seroconversion percentage (SCR) on day 56 (4 weeks after first injection) defined as the proportion of subjects reaching a $PRNT_{50}$ titre[2] $\geq$ 1/10;

The non-inferiority was accepted if the lower 95%CI limit of the difference in seroconversion percentages (IXIARO minus JE-VAX) was greater than -10%.

- geometric mean titre (GMT) on day 56 determined using a plaque reduction neutralisation test.

The non-inferiority was accepted if the lower 95%CI limit of the geometric mean titre ratio between IXIARO and JE-VAX (IXIARO/JE-VAX) was greater than a ratio of 1/1.5.

Results (see table 1):
- The seroconversion percentage was similar in both groups (IXIARO: 96.4% vs JE-VAX: 93.8%; 95%CI 1.05% [-1.33; 3.43]) on day 56.

The lower confidence interval limit of the difference between the seroconversion percentages (-1.33%) was greater than the predefined limit of -10% in the PP population.
- The geometric mean titre was 244 in the IXIARO group and 102 in the JE-VAX group on day 56.

The lower confidence interval limit of the geometric mean titre ratio (1.97) was greater than 1/1.5 in the PP population.

Table 1 – Study IC51-301: Seroconversion percentage and geometric mean titres on day 56 (PP)

day 56	seroconversion n (%)	**Estimated difference in risk (%)** 95%CI CI	GMT (n)	**Estimated GMT ratio** 95%CI
IXIARO	352/365 (96.4)	1.05 [-1.33; 3.43]	244 (361)	2.3 [1.97; 2.75]
JE-VAX	347/370 (93.8)		102 (364)	

Consequently, the non-inferiority of IXARIO compared to JE-VAX was demonstrated on day 56 in terms of seroconversion percentage and geometric mean titre.

3.1.2. Study IC51-303

Non-comparative extension of studies IC51-301 and IC51-302[3], the primary objective of which was to evaluate the immunogenicity of IXIARO 24 months after the first vaccination in subjects given at least one injection of IXIARO.
As the complete analysis at 24 months is not yet available, only the results at 6 and 12 months after the first vaccination will be presented.

Primary endpoint: seroconversion percentage (SCR) 24 months after the first vaccination

Results (see table 2):
At the 12 month intermediary analysis, the seroconversion percentage was 83.4%. The decrease in geometric mean titre observed over time was as expected and was comparable to the data observed with other inactivated Japanese encephalitis vaccines. Only the studies (currently in progress) evaluating the effect of a booster dose could determine whether this decrease has any clinical consequence.

[2] $PRNT_{50}$ (plaque reduction neutralisation test): responsible for inhibiting 50% of virus plaques.
[3] For study description refer to paragraph 3.2. Safety.

Table 2 – Seroconversion percentages and geometric mean titres at 6 and 12 months (ITT)

IXIARO N=181	SCR n (%)	95% CI	GMT	95% ICCI
at 6 months	172 (95.0)	[90.82; 97.36]	83.5	[70.89; 98.38]
at 12 months	151 (83.4)	[77.33; 88.14]	41.2	[34.39; 49.33]

3.1.3. Study IC51-308[4]

Randomised, single-blind study aiming to demonstrate both:
- the non-inferiority of the vaccine combination IXIARO+HAVRIX[5] compared to IXIARO+placebo in terms of geometric mean titre of Japanese encephalitis antibodies (JE antibodies) on day 56;
- the non-inferiority of the vaccine combination IXIARO+HAVRIX compared to HAVRIX+placebo in terms of geometric mean titre of hepatitis A antibodies (HAV antibodies) on day 28.

Vaccination schedule (IM administration):
- group A: two injections of IXIARO (6 µg) on day 0 and day 28 and one placebo injection on day 0;
- group B: one injection of HAVRIX 1440 (1 ml) on day 0 and two placebo injections on day 0 and day 28;
- group C: two injections of IXIARO (6 µg) on day 0 and day 28 and one injection of HAVRIX 1440 (1 mL) on day 0.

Primary endpoints (4 weeks after last injection):
- geometric mean titre of JE antibodies on day 56;
- geometric mean titre of HAV antibodies on day 28.

Non-inferiority was attained if the lower 95%CI limit of the IXIARO+HAVRIX/IXIARO +placebo geometric mean titre ratio and the IXIARO+HAVRIX/HAVRIX+placebo ratio was greater than 0.5.

Secondary endpoints:
- JE seroconversion percentage on day 56 defined as the percentage of patients showing a JE antibody titre greater than 1/10;
- HAV seroconversion percentage on day 28 defined as the percentage of patients showing an HAV antibody titre greater than 20 mIU / mL.

Results (see tables 3 and 4):
In all, 192 subjects were included: 65 in the IXIARO+placebo group, 65 in the HAVRIX+placebo group and 62 in the IXIARO+HAVRIX group.
Four weeks after the last injection of IXIARO, the lower confidence interval limit of the GMT ratio (0.75) was greater than 0.5. The geometric mean titre of JE antibodies in the IXIARO+HAVRIX group was not lower than that of the IXIARO+placebo group (table 3).

[4] Kaltenböck A, Dubischar-Kastner K et al. Safety and immunogenicity of concomitant vaccination with the cell-culture based Japanese Encephalitis vaccine IC51 and the hepatitis A vaccine HAVRIX1440 in healthy subjects: A single-blind, randomized, controlled Phase 3 study. Vaccine. 2009 Jul 16;27(33):4483-9.
[5] HAVRIX: inactivated hepatitis A vaccine

Table 3 - Geometric mean titres and seroconversion percentages of JE antibodies on day 56 (PP)

day 56	**GMT (n)**	**95%CI**[5]	**seroconversion %**
Group C (n=58): IXIARO + HAVRIX	202.7 (58)	[153.7; 261.2]	100
Group A (n=58): IXIARO + placebo	192.2 (55)	[147.9; 249.8]	98.2
GMT ratio (group C / group A)	1.05	[0.75; 1.47]	/

Four weeks after the injection of HAVRIX, the lower confidence interval limit of the GMT ratio (0.81) was greater than 0.5. The geometric mean titre of HAV antibodies in the IXIARO+HAVRIX group was not lower than that of the HAVRIX+placebo group (table 4).

Table 4 – GMT and seroconversion percentage of HAV antibodies on day 28 (PP)

day 28	**GMT (n)**	**95%CI**	**seroconversion %**
Group C (n=58): IXIARO + HAVRIX	24 (58)	[19.1; 30.1]	100
Group B (n=52): HAVRIX + placebo	21.7 (52)	[17.2; 27.5]	96.2
GMT ratio (group C / group B)	1.10	[0.81; 1.50]	/

Consequently, simultaneous vaccination with IXIARO and HAVRIX was not inferior to vaccination with IXIARO alone and HAVRIX alone in terms of geometric mean titre.

3.2. Adverse effects

3.2.1. Safety one month after last injection: study IC51-302[6]

Randomised, double-blind, placebo-controlled study involving 2,683 subjects over the age of 18, the primary objective of which was to evaluate the tolerance of IXIARO over a vaccination period of 28 days and up to 4 weeks after the last injection.

Vaccination schedule (IM administration):
- IXIARO 6 µg group: 2 doses administered on day 0 and day 28,
- placebo group: 2 doses administered on day 0 and day 28.

Primary endpoints:
- percentage of patients having had at least one serious adverse event;
- percentage of patients having had at least one adverse event requiring medical supervision.

Results (see table 5):
0.5% of the patients vaccinated with IXIARO had a serious adverse event versus 0.9% of the placebo patients (NS)
All the serious events occurring in the IXIARO group were considered to be “most likely unrelated” or “unrelated” to the vaccine.
Adverse events requiring medical supervision occurred in 12.7% of patients in the IXIARO group and 12.2% of those in the placebo group (NS).

[6] Tauber E, Kollaritsch et al. Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial of the Safety and Tolerability of IC51, an Inactivated Japanese Encephalitis Vaccine. JID. 2008; 198 :493-9

Table 5 - Patients having had at least one adverse event (AE)

	IXIARO N=1993 n (%)	**Placebo** N=657 n (%)	**p value**
AE	1,173 (58.9)	372 (56.6)	NS
AE requiring medical supervision	254 (12.7)	80 (12.2)	NS
Serious AE	10 (0.5)	6 (0.9)	NS
Severe AE	102 (5.1)	34 (5.2)	NS
AE related to treatment	774 (38.8)	254 (38.7)	NS
AE leading to termination of treatment	12 (0.6)	5 (0.8)	NS
Death	0	0	-

The most frequent adverse events were similar for IXIARO and the placebo: headaches (28.0% vs. 26.3%), myalgia (15.6% vs. 15.5%), flu-like syndrome (12.4% vs. 11.9%) and fatigue (11.4% vs. 11.7%).
The adverse events were mild in 33.7% of patients in the IXIARO group versus 34.1% of those in the placebo group. In each group, around 5% of patients had a severe adverse event.

3.2.2. Safety 6 months after last injection: pooled analysis among 4,715 adults

Adverse events were reported in around 64% of subjects in each group (IXIARO: 2,281/3,558, JE-VAX: 279/435, placebo: 8/657 except for the HAVRIX group (47.7%, i.e. 31/65).
Severe reactions were reported among around 4 to 7% of subjects, depending on the vaccination (IXIARO: 5.8%, i.e. 207/3,558; JE-VAX: 4.4%, i.e. 19/435; placebo: 6.4% i.e. 42/657; HAVRIX: 4.6%, i.e. 3/65).
Systemic reactions considered as attributable to the vaccine (headaches, myalgia, fatigue, flu-like syndrome) were reported for less than 40% of patients for IXIARO (38.3%, i.e. 1,352/3,558), JE-VAX (34.3%, i.e. 149/435) and the placebo (38.8%, i.e. 255/657) and in 18.5% of patients in the HAVRIX group (12/65).
Local reactions were reported at a comparable frequency during the week following administration of the 1st dose of IXIARO (47.9%), JE-VAX (45.7%) and the placebo (47.6%). These reactions were less frequent during the week following administration of the 2nd dose of IXIARO (29.8%) than with JE-VAX (42%) and the placebo (33.7%).

3.2.3. Safety 2 to 12 months after last injection: study IC51-303 (follow-up of studies IC51-301 and IC-51-302)

At least one adverse event was reported for 33.9% of subjects (61/180). Most of these events were mild to moderate. No event was considered to be treatment-related.
One severe adverse event was reported for 3 subjects (1.7%). No deaths were reported.

3.3. Conclusion

The immune response induced by the IXIARO vaccine (2 injections) was not inferior to that of the JE-VAX vaccine (3 injections) in terms of seroconversion percentage (96% vs. 94%; 1.05 95%CI [-1.33; 3.43]) and in terms of geometric mean titre (244 vs. 102; 2.3 95%CI [1.97; 2.75]) four weeks after the last injection in adults.

In a non-comparative extension study, the seroconversion percentage was around 80% during the intermediary 12-month analysis. The decrease in geometric mean titre observed over time was as expected and was comparable to the data observed with other inactivated Japanese encephalitis vaccines.

The geometric mean titre after simultaneous administration of the IXIARO and HAVRIX vaccines was not lower than that of IXIARO alone or HAVRIX alone.

The frequency and severity of the adverse events were generally comparable between IXIARO, JE-VAX and the placebo. The most commonly reported adverse events with IXIARO were headaches and myalgia.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

This vaccine prevents against inflammatory infections due to Japanese encephalitis viruswith a serious prognosis. Asymptomatic forms are common – on average, one case in every 250 is symptomatic. The serious forms can result in death or permanent neurological or psychiatric damage in 30% of survivors[7].

These products come under the scope of preventive treatment.

The efficacy (immunogenicity)/adverse effects ratio for these products is high.

There is no alternative validated vaccine.

> Public health benefit:
> The public health burden of Japanese encephalitis (JE) is low due to the limited number of patients concerned *(expatriates and those travelling in the area where the virus is present)*.
>
> Improved management and prevention of this disease do not constitute a public health need in France.
>
> Given the data available (non-inferiority in terms of immunogenicity, particularly compared to the JE-VAX vaccine, comparable safety, absence of morbidity and mortality data), no further impact is expected in terms of morbidity and mortality for IXIARO.
>
> Consequently, IXIARO is not expected to benefit public health in this indication.

The actual benefit of this vaccine is substantial in the populations recommended by the High Council for Public Health.

4.2. Improvement in actual benefit

Taking into account:

- the severity of the infections due to the Japanese encephalitis virus,
- the immunogenicity of this vaccine,
- the absence of any alternative benefiting from an MA,

IXIARO provides an important improvement in actual benefit (IAB II) in the prevention of Japanese encephalitis in adults in the populations recommended by the High Council for Public Health.

[7] Japanese encephalitis vaccination guidelines, report from the workgroup of the committee for travel-related diseases and imported diseases and the technical committee on vaccination, HCPH, April 2009.

4.3. Therapeutic use

Opinion of the High Council for Public Health of April 24, 2009 regarding guidelines for vaccination against Japanese encephalitis (see full HCPH opinion enclosed).

“Pending the results of studies on children, the High Council for Public Health recommends vaccination against Japanese encephalitis in regions where the virus is present for:

- expatriates or those who must stay for more than 30 days, over the age of 18,
- all travellers aged over 18 with a substantial amount of outdoor activity, particularly in rice field or marshy areas, during the period of the virus’ transmission, particularly during the wet season, regardless of the duration of stay. The following activities are considered to be high risk: sleeping outdoors without a mosquito net, camping, working outdoors, cycling, hiking, etc. particularly in areas where flood irrigation is practised.

The High Council for Public Health does not recommend systematically vaccinating travellers outside these situations.

The High Council for Public Health repeats the importance of individual measures to protect against mosquito bites:

- protection by skin repellents,
- wearing light-weight skin-covering clothes soaked in insect repellent (loose clothes, long sleeves, trousers and closed shoes) in the evening,
- sleeping under a mosquito net soaked in insect repellent.

The High Council for Public Health recommends that the Japanese encephalitis vaccine be made available only in international vaccination centres to evaluate the individual risk and facilitate pharmacovigilance monitoring.

These recommendations may be reviewed as the epidemiological situation evolves and according to changes in the marketing authorisation.

The main countries concerned (in whole or part) (see appendix 1) are:

Bangladesh, Cambodia, continental China and Hainan island, South Korea, North Korea, Hong Kong SAR, India, Japan, Laos, Malaysia, Myanmar, Nepal, Russia (Eastern Siberia), Sri Lanka, Taiwan, Thailand, Vietnam and more recently, the Northernmost part of Australia, Indonesia, Papua New Guinea, Pakistan, the Philippines, and East Timor”.

4.4. Target population

The target population of IXIARO is:

- expatriates or those who must stay for more than 30 days in the regions where the virus is present, over the age of 18,
- all travellers to regions where the virus is present aged over 18, with a substantial amount of outdoor activity, particularly in rice field or marshy areas, during the period of the virus’ transmission, particularly during the wet season, regardless of the duration of stay. The following activities are considered to be high risk: sleeping outdoors without a mosquito net, camping, working outdoors, cycling, hiking, etc. particularly in areas where flood irrigation is practised.

The target population cannot be calculated as:

- vaccination against Japanese encephalitis is not recommended systematically to all travellers to the regions where the virus is present,
- epidemiological data to specifically estimate the number of travellers over the age of 18 to be vaccinated is not available.

Furthermore, 1,500 nominative provisional licences were granted in 2006 for the JE-VAX vaccine used in the prevention of Japanese encephalitis and 1,700 in 2007.
Based on this information, the target population of IXIARO can be approximated by the number of provisional licences, i.e. at least 1,600 people.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indications, dosages of the MA and populations recommended by the High Council for Public Health in its opinion of April 24, 2009 (see enclosed).

4.5.1. Packaging:
The packaging is appropriate for prescription requirements.