HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

7 May 2014

IXIARO, suspension for injection

B/1 0.5 ml pre-filled glass syringe (CIP: 34009 393 959 7 5)

Applicant: NOVARTIS VACCINES AND DIAGNOSTICS SAS

INN	Inactivated Japanese encephalitis virus, strain SA(14)-14-2
ATC code (2013)	J07BA02 (encephalitis vaccines)
Reason for the review	**Extension of indication**
List concerned	**Hospital use (French Public Health Code L.5123-2)**
Indication concerned	"IXIARO is indicated for active immunisation against Japanese encephalitis in adults, **adolescents, children and infants aged 2 months and older."**

Actual Benefit	**Substantial for active immunisation against Japanese encephalitis in children from 2 months to 18 years of age only in populations recommended by the High Council for Public Health.**
Improvement in Actual Benefit	**Taking into account:** **- the severity of infections due to the Japanese encephalitis virus,** **- the absence of an alternative with Marketing Authorisation,** **and despite the very limited immunogenicity data in non-endemic areas, IXIARO provides a substantial improvement in actual benefit (level II) in the prevention of Japanese encephalitis in children (from 2 months to 18 years of age) in the populations recommended by the High Council for Public Health (HCPH).**
Therapeutic use	**IXIARO is the only vaccine currently indicated for active immunisation against Japanese encephalitis from the age of 2 months. The Transparency Committee stresses that the available immunogenicity and safety data in paediatric populations are limited in infants of less than 12 months of age. This vaccine must be used in accordance with the recommendations of the High Council for Public Health. This vaccination must be complemented by individual measures for protection against mosquito bites (skin repellents, skin-covering clothes soaked in insecticide, especially in the evening, and mosquito nets soaked in insecticide).**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised procedure)	Dates: 31/03/2009, 18/02/2010 (booster dose for adults) and 01/02/2013 (extension of the indication starting from 2 months)
Prescribing and dispensing conditions/special status	List I
ATC Classification	2013 J Antiinfectives for systemic use J07 Vaccines J07A Viral vaccines J07AB Encephalitis vaccines J07AB02 encephalitis, Japanese, inactivated, whole virus

02 BACKGROUND

IXIARO has Marketing Authorisation (centralised procedure) for the active immunisation of adults against Japanese encephalitis. In this indication, the Transparency Committee granted IXIARO a substantial actual benefit with a level II improvement in actual benefit on 23 September 2009, with the following argument:
“Taking into account:

- the severity of infections due to the Japanese encephalitis virus,
- the immunogenicity of this vaccine,
- the absence of an alternative with a Marketing Authorisation,

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

Since the assessment by the Committee in 2009, the SPC has been modified to recommend a booster dose in adults during the second year after the primary vaccination (amendment to the Marketing Authorisation on 18/02/2010 and vaccine schedule of 2011).

Within the framework of the paediatric investigation programme, this vaccine was granted an extension of the indication to infants aged 2 months and older, children and adolescents on 1 February 2013; this is the subject of this opinion.

The company is requesting inclusion on the list of medicines approved for use by hospitals so that this vaccine would be available in approved international vaccination centres.

03 THERAPEUTIC INDICATIONS

“IXIARO is indicated for active immunisation against Japanese encephalitis in adults, **adolescents, children and infants aged 2 months or older.**

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

04 DOSAGE

"Dosage
Adults
The primary vaccination 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.
It is recommended that vaccinees who received the first dose of IXIARO complete the primary 2-dose vaccination course with IXIARO.
In individuals who only receive a single dose as the primary vaccination, full protection against the disease might not be achieved. There are data that indicate that a second injection given up to 11 months after the first dose results in high seroconversion rates (see section 5.1).
Booster dose (adults)
A booster dose (third dose) should be given within the second year (i.e. 12-14 months) after the recommended primary immunisation, prior to potential re-exposure to the Japanese encephalitis virus (JEV). Persons at continuous risk for acquiring Japanese encephalitis (laboratory personnel or persons residing in endemic areas) should receive a booster dose 12 months after primary immunisation (see section 5.1). Data on the need for further booster doses are not available.

Children and adolescents from 3 to 18 years of age:
The primary vaccination 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.

Children aged from 2 months to 3 years of age:
The primary vaccination consists of two separate doses of 0.25 ml each, according to the following schedule:

- First dose: day 0
- Second dose: 28 days after the first dose.

See section 6.6 of the SPC for the instructions on preparing the 0.25 ml dose for children aged 2 months to < 3 years.
It is recommended that vaccinees who received the first dose of IXIARO complete the primary 2-dose vaccination course with IXIARO.

Children below 2 months of age:
The safety and efficacy of IXIARO in children younger than 2 months have not been established. No data are available.
Booster dose (children and adolescents)
Data on the timing of and response to a booster dose in children and adolescents (< 18 years of age) are not available.

Method of administration:
The vaccine should be administered by intramuscular injection into the deltoid muscle. In infants, the anterolateral aspect of the thigh may be used as the injection site. IXIARO 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 "Special warnings and precautions for use"). However, it should be noted that there are no clinical efficacy data to support administration by the subcutaneous route."

05 INTERACTIONS WITH OTHER VACCINES

No data on the administration of IXIARO with vaccines included in the vaccine schedule are available. Indeed, the SPC states that no interaction studies have been carried out in children and adolescents. Studies to evaluate the co-administration of IXIARO with other vaccines are underway (see section 10.4: Planned studies).

06 THERAPEUTIC NEED[1,2,3]

Japanese encephalitis is a viral disease due to infection with a flavivirus (family of viruses to which dengue, yellow fever and chikungunya belong) transmitted by the bite of mosquitoes of the genus Culex, which are active at night, with peaks of activity at dusk and at dawn.
This viral infection is mainly present in Asia. Wild birds form the reservoir of infection. The pig is the main amplifying host, and humans remain an accidental host, mainly bitten when the populations of infected mosquitoes become very large.
In areas where it is endemic, infection mainly occurs in young children. In fact, older children and adults who have been infected in the past acquire permanent immunity.
The disease is very rare among travellers and can occur at any age. However, among expatriates and travellers who stay for prolonged periods in rural areas where the transmission of the Japanese encephalitis virus is active, the risk of Japanese encephalitis may reach levels similar to those among the local population.
The principal tropism of Japanese encephalitis is the central nervous system. Asymptomatic forms predominate. There is on average one symptomatic case for every 250 infections. It is mainly children and young adults who are affected. After an incubation period of 5 to 15 days, the clinical picture comprises fever, meningeal signs (nausea, vomiting, stiff neck, photophobia) and signs of acute encephalitis (stupor, disorientation, coma, tremor, convulsions, paralysis). Children with the disease are at greater risk of developing focal or generalised convulsions (50-85% of cases, as opposed to 10% in adults). The disease, when it is symptomatic, may leave permanent neurological or psychiatric sequelae (abnormal movements, convulsions, paralysis, mental retardation) in 30 to 50% of cases and leads to death in 20 to 30% of cases. The sequelae appear to be more severe in children.[4]

There is no specific treatment for Japanese encephalitis. It is important to take individual precautions for protection against mosquito bites (skin repellents, skin-covering clothes soaked in insecticide).

[1] Orphanet: Japanese encephalitis.
[2] Centers for Disease Control and Prevention. Chapter 3. Infectious Diseases Related to travel. In: Health Information for International Travel 2014. New-York, Oxford University Press, 2014.
http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/japanese-encephalitis.
[3] Opinion on the recommendations relating to vaccination against Japanese encephalitis with the vaccine IXIARO, HCPH, 20 September 2013 http://www.HCPH.fr/Explore.cgi/avisrapportsdomaine?clefr=381.
[4] Halstead SB, Thomas SJ. Japanese Encephalitis: New Options for Active Immunization. Clin Infect Dis. 2010; 50(8): 1155-64.

07 CLINICALLY RELEVANT COMPARATORS

07.1 Medicinal products

There is no other vaccine for the prevention of Japanese encephalitis that has Marketing Authorisation in Europe.

Conclusion

There is no clinically relevant comparator.

08 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	Marketing Authorisation	
	YES/NO	Populations
USA	Yes (30/03/2009 and 05/2013)	From 2 months
Singapore	Yes (16/02/2012)	
Hong Kong	Yes (08/10/2010)	
Australia	Yes (23/01/2009)	In adults over 18 years old (proprietary medicinal product JESPECT, CSL
Canada	Yes (30/10/2009)	In adults over 18 years old
Israel	Yes (29/05/2011)	
Macau	No (temporary authorisation for importation 01/2011)	
Switzerland	Yes (06/05/2010)	
New Zealand	Yes (18/10/2012)	

09 SUMMARY OF PREVIOUS ASSESSMENTS

Date of opinion (reason for request)	Opinion of 23 September 2009 (Inclusion on the list of medicines approved for hospital use)
Indication	IXIARO is indicated for active immunisation against Japanese encephalitis in adults. IXIARO should be considered for use in individuals at risk of exposure by the virus through travel or in the course of their occupation.
Actual Benefit	**Substantial AB** The actual benefit of this vaccine is substantial in the populations recommended by the High council for Public Health, that is to say, in the regions where the virus is present, for: • all expatriates and those who must stay for more than 30 days who are over the age of 18, • all travellers over 18 with a substantial amount of outdoor activity, particularly in rice fields of 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.
Improvement in Actual Benefit	**IAB II** Taking into account: - the severity of infections due to the Japanese encephalitis virus, - the immunogenicity of this vaccine, - the absence of a substantial alternative with a MarketingAuthorisation, IXIARO provides a substantial improvement in actual benefit (level II) in the prevention of Japanese encephalitis in adults in the populations recommended by the high council for Public Health.

010 ANALYSIS OF AVAILABLE DATA

In support of its application, the company presented the results of two phase III studies to evaluate the safety and immunogenicity of IXIARO in children between 2 months and 18 years of age (see Table 1):

- in endemic areas: comparative study IC51-323
- in non-endemic areas: non-comparative study IC51-322

Table 1: Summary of two phase III studies in paediatric populations

Study	Primary endpoint:	Vaccination groups	N total/ N IXIARO	Country
IC51-323 comparative open-label	safety	IXIARO 0.5 ml 2 IM injections (D0 and D28) in subjects ≥ 3 years old or IXIARO 0.25 ml 2 IM injections (D0 and D28) in subjects < 3 years old *Versus* HAVRIX 720 UI 2 injections on D0 and in M7 for subjects [1 year;18 years[or PREVENAR 0.5 ml 3 or 4 injections depending on age: [2 months;6 months[: D0, D28, D56 and M7 [6 months;1 year[: D0, D56 and M7	1869/1411	Endemic area: Philippines
IC51-322 non-comparative open-label ***Interim results***	safety	IXIARO 0.5 ml 2 IM injections (D0 and D28) in subjects ≥ 3 years old or IXIARO 0.25 ml 2 IM injections (D0 and D28) in subjects < 3 years old	60/60	Non-endemic area: EU, USA, Australia

010.1 Safety and immunogenicity

10.1.1 Study IC51-323 in endemic areas[5]

Randomised, open-label study the principal objective of which was to evaluate the safety of the IXIARO vaccine (two injections) in comparison with PREVENAR (7-valent pneumococcal conjugate vaccine) or HAVRIX 720 (hepatitis A vaccine) in 1869 children between 2 months and 18 years of age living in endemic areas (Philippines). The immunogenicity of IXIARO was evaluated in a subgroup of subjects (496/1869). An additional objective was to establish the appropriate dose of IXIARO (0.25 or 0.50 ml) in the 3-12 year age range.

Vaccination scheme (see Table 2):
Randomisation was stratified according to age at inclusion.
The subjects were randomly assigned to one of the following groups:

- IXIARO group: two IM injections of 0.25 or 0.50 ml on D0 and D28

[5] Carried out between March 2010 and July 2011

It should be noted that the packaging for which the company is requesting inclusion on the list of medicines approved for hospital use (prefilled syringe graduated to indicate a half dose) was not tested in this study, the 0.25 ml dose was administered with the aid of a tuberculin syringe.

- Control group: PREVENAR[6] (3 or 4 doses) or HAVRIX 720[7] (two doses on D0 and in month 7).

In the absence of a phase II dose-finding study in children between 3 and 12 years of age, a dose-finding sub-study was carried out to determine the appropriate dose of IXIARO (0.25 or 0.50 ml) before the randomisation between IXIARO and HARIX 720. It should be noted that a dose-finding study (study IC51-221) carried out in an endemic area (India) led to the selection of a dose of 0.25 ml of IXIARO for children between 1 and 3 years of age.

Table 2: Vaccination scheme (study IC21-323)

Age	2 months – 1 year		1 – 3 years	3 – 12 years		12 – 18 years
Planned number of subjects	195		852	200**	300	320
Randomi-sation	2:1		3:1	1:1	2:1	3:1
Vaccin-ation groups	IXIARO 0.25 ml N = 131		IXIARO 0.25 ml N = 640	IXIARO 0.25 ml N = 100	IXIARO (dose adjusted as a function of age) N = 200	IXIARO 0.5 ml N = 240
	[2 - 6 months] PREVENAR 0.5 ml 4 doses: D0, D28, D56 and between 7 and 13 months*	[6 - 12 months] PREVENAR 0.5 ml 3 doses: D0, D56 and in month 7	HAVRIX 720 0.5 ml	IXIARO 0.5 ml	HAVRIX 720 0.5 ml	HAVRIX 720 0.5 ml
	N = 64		N = 213	N = 101	N = 100	N = 80

* So that the children were between 12 and 15 months old at the time of the 4th dose.

** Dose-finding sub-study carried out to determine the appropriate dose of IXIARO (0.25 or 0.50 ml).

Primary endpoint: Percentage of subjects with serious adverse events or medically expected adverse events, defined as each adverse event requiring medical intervention (consultation with a doctor, in the emergency department or in hospital) up to the 56th day after the first vaccination.

Among the secondary endpoints on D56 and in month 7:

- **Seroconversion rate (SCR)** defined as the proportion of subjects with an antiviral antibody titre against Japanese encephalitis ≥ 1/10 according to the $PRNT_{50}$;[8]
- Geometric mean titre (GMT): Mean neutralising antibody titre determined using a plaque reduction neutralisation test.

[6] The vaccine against invasive pneumococcal infections still recommended in France is a 13-valent pneumococcal conjugate vaccine (PREVENAR 13) with a 3-dose vaccination scheme according to the new vaccination schedule 2013:
- for children aged 2 to 6 months: one dose at 2 months and 4 months with a booster dose at 11 months;
- for children aged 7 to 11 months who have not previously been vaccinated: two doses with a two-month interval and a booster dose one year later.

[7] According to the health recommendations for travellers for 2013, the hepatitis A vaccine can be used at a dose of 720 units from 1 to 15 years of age and at a dose of 1440 units above 15 years of age.

[8] $PRNT_{50}$ (plaque reduction neutralisation test): results in 50% inhibition of viral plaques.

Results
A total of 1869 subjects were randomised. The number of patients per treatment group is shown in Table 2, above.

Results for the primary endpoint: Safety (n = 1869)
The percentage of subjects with serious or medically expected adverse events up to D56 (primary endpoint) was similar in the different groups:

- 2 months to 1 year: IXIARO 0.25 ml: 38.2% and PREVENAR: 42.2%
- 1 to 3 years: IXIARO 0.25 ml: 26.7% and HAVRIX 720: 22.1%
- 3 to 12 years: IXIARO 0.25 ml: 7%, IXIARO 0.50 ml: 8% and HAVRIX 720: 5.9%
- 12 to 18 years: IXIARO 0.50 ml: 1.7% and HAVRIX 720: 3.8%.

A total of 11 subjects (0.6%) reported a serious adverse event on D56: 6 subjects in the IXIARO 0.25 ml group, 1 in the PREVENAR group and 4 in the HAVRIX 720 group. Those most frequently reported were febrile seizures (5 subjects). No serious adverse event was regarded as connected with the vaccine. Medically expected adverse events were reported in 339 subjects; the most frequent were infections of the upper respiratory tract and gastroenteritis.

In addition, the percentages of adverse events were comparable in the different vaccination groups in each age range. The majority were mild. The safety profile in children between 12 and 18 years of age was similar to that in adults.

Results for the secondary endpoints: Immunogenicity in a subgroup of subjects (n = 496 of 1869 subjects)
The seroconversion rates were between 99.2% and 100% on D56 and between 77.1% and 100% in the 7th month, depending on the dose of IXIARO and the age range under consideration (see Table 3).
Taking all age ranges together, the seroconversion rate for the two doses of IXIARO were comparable on D56 (0.25 ml: 98% 95% CI [95.9-98.6]) and 0.50 ml: 100% $CI_{95\%}$ [98.4-100]). In the 7th month, the seroconversion rates with the half dose were lower (83.9% $CI_{95\%}$ [80.6-86.1]) than with the 0.50 ml dose (94.5% $CI_{95\%}$ [91.9-95.7]).

The geometric means of the titres were between 113.89 and 457.93 on D56 and between 28.76 and 88.63 in the 7th month, depending on the dose and the age range under consideration (see Table 3).
Taking all age ranges together, the geometric means of the titres for the two doses of IXIARO were comparable on D56 (0.25 ml: 199.39 and 0.50 ml: 190.77). In the 7th month, the reduction in the geometric means of the titres was more pronounced following the half dose (37.99) than following the 0.50 ml dose (64.83).

In the 3-12 year age range, for which two doses of IXIARO were evaluated, a difference in terms of seroconversion and the geometric mean of titres was observed in favour of the 0.50 ml dose. Therefore, and in view of the similar safety data, the 0.50 ml dose is the one included in the Marketing Authorisation for this age group.

Table 3: Seroconversion rate and geometric mean of the titres for each dose and age, ITT (study IC51-323)

		IXIARO 0.25 ml			IXIARO 0.5 ml	
		2 months – 1 year N = 28	1 – 3 years N = 120	3 – 12 years N = 98	3 – 12 years N = 100	12 – 18 years N = 137
Seroconversion						
D56	n (%)	28 (100%)	119 (99.2%)	94 (95.9%)	100 (100%)	137 (100%)
	$CI_{95\%}$	87.9 - 100	95.4 - 99.9	90.0 - 98.4	96.3 - 100	97.3 - 100
M7	n (%)	28 (100%)	106 (85.5%)	74 (77.1%)	91 (91%)	133 (97.1%)
	$CI_{95\%}$	87.9 - 100	78.2 - 90.6	67.7 - 84.4	83.8 - 95.2	92.7 - 98.9
Geometric mean titre (GMT)						
D56	GMT	457.93	258.90	113.89	213.67	175.63
	$CI_{95\%}$	283.53 - 739.61	214.43 - 312.59	89.9 - 144.26	175.58 - 260.03	147.79 - 208.71
M7	GMT	88.63	38.91	28.76	43.60	86.61
	$CI_{95\%}$	61.49 - 127.77	31.75 - 47.67	22.64 - 36.54	35.58 - 53.43	70.74 - 106.04

In this study, carried out in endemic areas, subgroup analyses were performed as a function of immune status with respect to Japanese encephalitis virus and dengue virus at inclusion. At inclusion, 20.2% (100/496) of the subjects vaccinated with IXIARO were regarded as seropositive for the Japanese encephalitis virus: 7.5% (19/255) in the IXIARO 0.25 ml group and 33.6% (81/241) in the IXIARO 0.5 ml group. In addition, 46.6% of the subjects vaccinated with IXIARO were regarded as seropositive for dengue virus: 29.8% (76/255) in the IXIARO 0.25 ml group and 64.3% (155/241) in the IXIARO 0.5 ml group.
For information, these exploratory analyses showed that, by comparison with subjects who were naïve at inclusion, pre-existing immunity to the Japanese encephalitis virus was associated with:
- a lower geometric mean titre on D56 (for the IXIARO 0.50 ml groups)
- a higher seroconversion rate during the 7th month.

On the other hand, being seropositive to the dengue virus seems to have a negative effect on the antibody response after the administration of the second dose, but not in the 7th month.

10.1.2 Study IC51-322 – non-endemic areas

Non-comparative phase III study carried out in non-endemic areas (United States, Europe, Australia) in children and adolescents intending to travel in regions where Japanese encephalitis is endemic and where vaccination against the Japanese encephalitis virus is recommended.
The objective of this study was to evaluate the safety and immunogenicity of IXIARO administered as two IM injections (D0 and D28) at a dose of 0.25 ml in children between 2 months and 3 years of age and 0.50 ml in children and adolescents between 3 and 18 years of age.

The subjects included were to have been planning to travel to a area where Japanese encephalitis is endemic after the end of the completing the course of 2 vaccinations. Exposure to Japanese encephalitis was to be avoided for 1 week after administration of the second dose of IXIARO and subjects were to return to the non-endemic area before the 7 month appointment. The voyage to the endemic area was to take place between D35 and D56 or between D56 and the 7th month.

Only an interim analysis that was not specified in the protocol is available, and will be presented below for information.
Initially, it was planned to include 100 children and adolescents, but, because of the low rate of inclusion, it was decided to carry out an analysis with the data from the 60 subjects included in the study up to 30 September 2011.

Primary endpoint: Percentage of subjects with serious adverse events or medically expected adverse events, defined as each adverse event requiring medical intervention (consultation with

a doctor, in the emergency department or in hospital) up to the 56th day after the first vaccination. In the initial protocol, the primary endpoint was immunogenicity. Following a protocol amendment on 20 September 2011 (immediately before closure of the database), this primary endpoint was replaced by a safety endpoint.

Secondary endpoints on D56:
- Seroconversion rate (SCR) defined as the proportion of subjects with an antiviral antibody titre against Japanese encephalitis ≥ 1/10 according to the $PRNT_{50}$;[8]
- Geometric mean titre (GMT): Mean neutralising antibody titre determined using a plaque reduction neutralisation test.

Results:
The median age of the subjects at baseline was 15.2 years: 1.1 years in the IXIARO 0.25 ml group (n = 5) and 15.5 years in the IXIARO 0.5 ml group (n = 55). Only 5 children were between 2 months and 3 years of age, and 14 between 3 and 14 years of age.

Results for the primary endpoint: safety
On non-protocol analysis, 60 subjects had received one dose of IXIARO and 56 had received the second dose (93.3%).
For information, no serious adverse events had been observed up to D56. Three children (5%) had reported mild to moderate medically expected adverse events.
The available data are very limited, particularly for the 0.25 ml dose of IXIARO, so no conclusions can be drawn about the safety of IXIARO in children less than 3 years old in non-endemic areas.

Results for the secondary endpoints
The immunogenicity data obtained by the time of the non-protocol analysis are presented, for information, in the table below. It should be noted that ITT data are only available for 51 subjects up to D56 and 18 up to month 7.

Table 4: Seroconversion rate (SCR) and geometric mean titre (GMT) as a function of dose, ITT (study IC51-322)

Group	Time	SCR	GMT [95% CI]
IXIARO 0.25 ml 2 months – 3 years	D56	5/5 (100%)	216.2 [106 - 441]
	Month 7	2/2 (100%)	48.0 [0 – 3214485.7]*
IXIARO 0.5 ml 3 – 18 years	D56	46/46 (100%)	332,1 [251.2 – 439.0]
	Month 7	16/16 (100%)	84.0 [56.3 – 125.4]

* Data for month 7 are only available for 2 subjects in the IXIARO 0.25 ml group, with GMTs of 20 and 115.

010.2 Other safety data

The SPC states that: “The safety of IXIARO was assessed in controlled and uncontrolled clinical studies in 4248 healthy adults (from non-endemic countries) and 1371 children and adolescents (from endemic countries).
Approximately 40% of treated subjects experienced systemic adverse reactions and approximately 54% experienced injection site reactions. They usually occur within the first three days after vaccination, are usually mild and resolve within a few days. No increase in the number of adverse reactions was noted between first and second doses or following a booster dose.
Most commonly reported adverse reactions included headache (20% of subjects) and myalgia (13%).”

The adverse effects reported most often (> 10%) were:

- in children (from 2 months to 3 years old) given the 0.25 ml dose: pyrexia (28.9%), diarrhoea (11,8%), flu-like syndrome (11.2%), irritability (11%). These undesirable events are observed more frequently than in children over 3 years of age, adolescents, and adults;
- in children and adolescents (from 3 months to 18 years old) given the 0.50 ml dose: pain at the injection point (12.2%), pyrexia (11.3%).

The adverse events that received the most attention in the RMP are as follows:

- Allergic reactions:
  - Identified major risk: dermatitis, dyspnoea, erythema, ocular pruritus, flush, hypersensitivity, pruritus, rash, urticaria
  - Potential major risk: conjunctivitis, hypotension.
- Neurological adverse events:
  - Identified major risk: seizure
  - Potential major risk: acute disseminated encephalomyelitis, acute encephalitis, acute myelitis inflammation of the central nervous system, Guillain-Barré syndrome.

Finally, the High Council for Public Health recommends that an enhanced pharmacovigilance programme should be set up by the ANSM [French National Health Products Safety Agency].

010.3 Summary & discussion

The available data in support of the extension of the indication for IXIARO to the prevention of Japanese encephalitis in paediatric populations (from 2 months of age) are limited, particularly in infants under 12 months old. They are based mainly on study IC51-323, which was carried out in endemic areas.
This randomised, open-label study, which had as its principal objective the evaluation of the safety of the IXIARO vaccine (two injections) in comparison with PREVENAR (7-valent pneumococcal conjugate vaccine) or HAVRIX 720 (hepatitis A vaccine), was carried out in 1869 children between 2 months and 18 years of age living in endemic areas (Philippines).
The percentages of serious adverse events or medically expected adverse events up to D56 (primary endpoint) were similar, in each age group, for IXIARO and the vaccines PREVENAR or HAVRIX 720. The majority of adverse events were mild.
The immunogenicity was evaluated as a secondary endpoint in a subgroup of 496 subjects out of 1869. Despite the low level of evidence, the immune response induced by two injections of IXIARO at the dose adjusted according to age (0.25 or 0.50 ml) was good in terms of the seroconversion rate (≥ 99.2%) and the geometric mean titre (from 175.63 to 457.93) at D56, whatever the age of the subjects. A reduction in the seroconversion rate (≥ 85.5%) and the geometric mean titre (from 38.91 to 88.63, depending on age) was observed at 7 months. The persistence of immunity in the paediatric population after administration of two doses with a one-month interval is not known. Effectively, the additional data permitting the evaluation of the benefit of a booster dose are not yet available.

The data in children and adolescents intending to travel to endemic areas where vaccination against the Japanese encephalitis virus is recommended are still very limited.

Data relating to the simultaneous administration of IXIARO and other paediatric vaccines recommended for travellers are not available.

010.4 Planned studies

Several studies that were organised on the initiative of the company and which mainly relate to the long-term safety are underway:

Study	Objectives	Time frame
IC51-401	Surveillance study of safety: programme of the United States Department of Defense: safety of IXIARO in 20,000 American soldiers + monitoring of cases of pregnancy	Start: 2011 Results: Q3 2014
V59-38	Co-administration of MENVEO/IXIARO	Started in Q1 2012 Results: 2014
V49-23	Co-administration of rabies vaccine/IXIARO, including a short course of vaccinations	Start: August 2012 Results: Q3 2014
IC51-324	Long-term immunity [persistence] in the endemic area: subjects who completed study IC51-322/follow-up after 3 years	Start: 2011 Results: Q2 2015
C51-325	Long-term immunity [persistence] and immunogenicity of a booster dose in the endemic area	Start: 2011 Results: Q3 2014

011 THERAPEUTIC USE

According to the opinion updated on 20 September 2013 in relation to vaccination against Japanese encephalitis with the vaccine IXIARO,[3] the High Council for Public Health:

- "does not recommend systematic vaccination against Japanese encephalitis of all travellers visiting Asia or Oceania;
- recommends vaccination with the vaccine IXIARO of persons more than 2 months of age in the following circumstances:
  - sojourn (whatever the duration) with exposure to the outside environment,[9] in an endemic area (see map), in particular in rural areas;[10]
  - expatriation to a country in the region where the virus is present;[11]
  - any other situation judged to be high risk by the vaccinating doctor.

The HCPH also repeats the importance of individual measures to protect against mosquito bites (skin repellents, mosquito nets soaked in insect repellent and clothes soaked in insect repellent).

[9] High-risk activities : camping, cycling, hiking, working outdoors, particularly in areas where flood irrigation is practised.
[10] Areas where flood irrigation is practised (rice fields), close to pig farms, at times of epidemics (or of increased circulation of the virus in animals in countries with a high level of vaccination coverage in humans).
[11] The countries currently involved (all or some of their territory) (see map and table below) are the following: 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 extreme north of Australia, Indonesia, Papua New Guinea, Pakistan, Philippines and East Timor.

Rare cases having been reported in travellers who have not, in theory, left the urban environment, the HCPH requests that these recommendations to be revised regularly as a function of the development of the epidemiology of the disease.

The HCPH also requests that the data on the simultaneous administration of IXIARO and vaccines included in the vaccine schedule for children should be sent to it as soon as they become available.

The High Council for Public Health lastly recommends that an enhanced pharmacovigilance programme for the vaccine IXIARO should be set up by the ANSM."

Therapeutic use of IXIARO

IXIARO is the only vaccine currently indicated for active immunisation against Japanese encephalitis from the age of 2 months. The Transparency Committee stresses that the available immunogenicity and safety data in paediatric populations are limited in infants of less than 12 months. This vaccine should be used in accordance with the recommendations of the High Council for Public Health.[3] This vaccination must be complemented by individual measures for protection against mosquito bites (skin repellents, skin-covering clothes soaked in insecticide, especially in the evening, and mosquito nets soaked in insecticide).

012 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above data and information, and following the debate and vote, the Committee's opinion is as follows:

012.1 Actual Benefit

◗ Infections with the Japanese encephalitis virus are infections that may, in severe forms, lead to death in a third of cases or to permanent neurological or psychiatric sequelae in 50% of survivors. Asymptomatic forms are common, there is on average one symptomatic case for every 250 infections. In endemic areas, it is mainly children that are affected. The disease is very rare among travellers and can occur at any age.

◗ This proprietary medicinal product is intended as preventive therapy.

◗ Public health benefit:

Despite the severity of Japanese encephalitis, its importance for public health in France is low because of the limited number of cases reported among expatriates and travellers in the area where the virus is present, including in children between 2 months and 18 years of age.

The fight against the disease vector remains the principal means of reducing the transmission of Japanese encephalitis in the endemic area. In France, the prevention of this disease is not one of the established public health priorities. Individual vaccination, together with other preventive measures against mosquito bites, remains an essential component of the strategy for the prevention of Japanese encephalitis in the populations defined by the HCPH.

In light of the available data, which are limited in those less than 18 years of age and based mainly on a safety and immunogenicity study carried out in the endemic area, the impact of the proprietary medicinal product IXIARO on morbidity and mortality cannot be established.

Therefore, because of the low number of cases reported in France, it is not expected that this vaccine will have an impact on public health in this age range.

◗ The efficacy (immunogenicity)/adverse effects ratio is high.

◗ There are no vaccine alternatives with Marketing Authorisation in Europe.

Taking account of these points, the Committee considers that the actual benefit of IXIARO is substantial for active immunisation against Japanese encephalitis in children between 2 months and 18 years of age only in the populations recommended by the High Council for Public Health.

012.2 Improvement in actual benefit (IAB)

Taking into account:
- the severity of infections due to the Japanese encephalitis virus,
- the absence of an alternative with a Marketing Authorisation,

and despite the very limited immunogenicity data in non-endemic areas, IXIARO provides a substantial improvement in actual benefit (level II) in the prevention of Japanese encephalitis in children (from 2 months to 18 years of age) in populations recommended by the High Council for Public Health.

012.3 Target population

The target population of IXIARO in children and adolescents is made up of people 2 months old and above in the following circumstances:
- sojourn (whatever the duration) with exposure to the outside environment,[9] in an endemic area, in particular in rural areas;[9]
- expatriation to a country in the region where the virus is present;[11]
- any other situation judged to be high risk by the vaccinating doctor.

Epidemiological data that would permit estimation of the number of people under 18 years of age (new expatiates and travellers) who fall within the scope of vaccination are not available.

However, about 13,000 doses of IXIARO vaccine were sold for use in adults in 2012. These sales data correspond approximately to the vaccination of 4300 to 6500 travellers or expatriates (depending on whether or not the possibility that the booster dose was administered in the host country is taken into consideration). Taking all destinations together, the proportion of children vaccinated in a vaccination centre is estimated at 15 to 20% (according to expert opinion). However, systematic vaccination against Japanese encephalitis is not recommended for all travellers to regions where the virus is present, so the proportion of children eligible for vaccination is not known.

Taking account of all these factors, the target population cannot be estimated precisely.

013 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion on the list of medicines approved for hospital use in the indication, at the dosages in the Marketing Authorisation and in the populations recommended by the High Council of Public Health.

◗ Packaging

Children aged from 2 months to 3 years: The packaging has not been changed. In fact, packaging specifically adapted for the dosage in children less than 3 years old (0.25 ml) has not been developed (in accordance with the paediatric investigation plan[12]). Thus, only a syringe pre-filled with 0.5 ml is available, which comfortably exceeds the amount required for a 0.25 ml injection. A specific graduation mark (red line) shows the excess volume to be ejected before injection of the half dose. Thus, the risk of erroneous injection of a double dose (0.5 ml) cannot be ruled out.

Children aged from 3 to 18 years: The packaging has been adapted to the prescribing conditions according to the vaccination scheme recommended by the HCPH.

[12] EPAR for IXIARO of 13 December 2012, page 4/73.