KAMADA

דצמבר 2018

<u>רופא/ה, רוקח/ת נכבד/ה,</u>

חברת קמהדע מבקשת להודיע על עידכון מידע כמפורט להלן, עבור התכשיר:

IXIARO ; איקסיארו

Suspension for injection IM

מרכיבים פעילים בהתאם לרישיון:

JAPANESE ENCEPHALITIS PURIFIED INACTIVATED VACCINE 6 AU / 0.5 ML

התוויה:

Ixiaro is indicated for active immunization against Japanese encephalitis in adults, adolescents, children and infants aged 2 months and older.

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

מהות השינויים: עידכון משטר המינון, באישור משרד הבריאות.

העלון לרופא עודכן בסעיף 4.2 בהתאם. בנוסף עודכנו הסעיפים 4.8 ו-5.1 (מפורטים להלן רק תתי הסעיפים שבהם נעשו עיקר השינויים. טקסט חדש מודגש בקו תחתי ; מחיקות נעשו בקו חוצה. החמרות הודגשו בצהוב):

4.2 Posology and method of administration

<u>Posology</u>

Adults <u>(18-65 years of age)</u>

The primary vaccination series consists of two separate doses of 0.5 ml each, according to the following conventional schedule:
First dose at Day 0.
Second dose: 28 days after first dose.

Rapid schedule Adults 18-65 years of age:
Persons aged 18-65 years can be vaccinated in a rapid schedule as follows:
First dose at Day 0.
Second dose: 7 days after first dose.

With both schedules, primary immunisation should be completed at least one week prior to potential exposure to Japanese encephalitis virus (JEV) (see section 4.4).

It is recommended that vaccinees who received the first dose of IXIARO complete the primary 2-dose vaccination course with IXIARO.
If the primary immunization of two injections is not completed, full protection against the disease might not be achieved. There is data 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 - 24 months) after primary immunization, prior to potential re-exposure to JEV.
Persons at continuous risk for acquiring Japanese encephalitis (laboratory personnel or persons residing in endemic areas) should receive a booster dose at month 12 after primary immunization (see section 5.1). ~~Data on the need for further booster doses are not available.~~

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Long-term seroprotection data following a first booster dose administered 12 - 24 months after primary immunization suggest that a second booster should be given 10 years after the first booster dose, prior to potential exposure to JEV.

Elderly (≥ 65 years of age)
The primary vaccination series consists of two separate doses of 0.5 ml each, according to the following conventional schedule:
First dose at Day 0.
Second dose: 28 days after first dose.

The primary immunisation should be completed at least one week prior to potential exposure to Japanese encephalitis virus (JEV) (see section 4.4).

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

If the primary immunization of two injections is not completed, full protection against the disease might not be achieved.

As with many vaccines, the immune response in elderly persons (≥ 65 years of age) to IXIARO is lower than in younger adults. Duration of protection is uncertain in elderly persons, therefore the physician should take this into account when considering a booster dose (third dose) before any further exposure to JE virus.

Paediatric Population
Children and adolescents from 3 years to < 18 years of age
The primary vaccination series consists of two separate doses of 0.5 ml according to the following schedule:
First dose at Day 0.
Second dose: 28 days after first dose.

Children from 2 months to < 3 years of age
The primary vaccination series consists of two separate doses of 0.25 ml according to the following schedule:
First dose at Day 0.
Second dose: 28 days after first dose.

See section 6.6 for instructions on preparing a 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.

Booster dose (Children and adolescents)

A booster dose (third dose) should be given within the second year (i.e. 12 - 24 months) after primary immunization, prior to potential re-exposure to JEV.
Children and adolescents at continuous risk for acquiring Japanese encephalitis (residing in endemic areas) should receive a booster dose at month 12 after primary immunization (see section 5.1).

Children and adolescents from 3 years to < 18 years of age should receive a single 0.5 ml booster dose.
Children from 14 months to < 3 years of age should receive a single 0.25 ml booster dose.
See section 6.6 for instructions on preparing a 0.25 ml dose for children aged 2 months to <3 years.

No long-term seroprotection data beyond two years after a first booster administered 1 year after primary immunization has been generated in children.

Children below 2 months of age
The safety and efficacy of IXIARO in children younger than 2 months has 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.~~

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4.8 Undesirable effects

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Paediatric population (2 months to <18 years of age)

Table 1: Frequency of adverse reactions observed in children given the 0.25 ml dose (2 months to <3 years of age) and in children and adolescents given the 0.5 ml dose (3 years to <18 years of age)

	Frequency of adverse reactions(%) by dose/age	
System Organ Class Preferred Term	**0.25 ml** **N=~~771~~783** **2 months to <3 years**	**0.5 ml** **N=~~540~~628** **3 to <18 years**
Blood and Lymphatic System Disorders		
Lymphadenopathy	0.1	0.0
Metabolism and Nutrition Disorders		
Decreased appetite	8.2	~~2.0~~1.9
Nervous System Disorders		
Headache	~~3.0~~2.9	~~5.8~~6.1
Respiratory, Thoracic and Medistinal Disorders		
Cough	0.5	~~0.2~~0.3
Gastrointestinal Disorders		
Diarrhoea	~~11.8~~11.9	~~1.1~~1.4
Vomiting	~~7.4~~7.3	1.9
Nausea	~~4.0~~3.9	~~1.3~~1.9
Abdominal pain	0.1	0.0
Skin and Subcutaneous Tissue Disorders		
Rash	~~6.4~~6.3	~~0.9~~1.4
Musculoskeletal and Connective Tissue Disorders		
Myalgia	~~3.1~~3.0	~~3.2~~7.1
General Disorders and Administration Site Conditions		
Pyrexia	~~28.9~~28.5	~~11.3~~10.4
Influenza-like illness	~~11.2~~10.9	~~3.0~~2.9
Irritability	~~11.0~~10.9	~~1.1~~1.9
Fatigue	3.5	~~2.2~~3.5
Injection site redness	~~9.7~~10.0	4.1
Injection site pain	~~6.3~~6.1	~~12.2~~14.1
Injection site tenderness	4.2	~~8.9~~14.7
Injection site swelling	3.6	~~2.6~~2.2
Injection site hardening	~~1.0~~1.2	~~1.5~~1.9

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Injection site itching	0.6	~~1.1~~1.6
Investigations		
Hepatic enzymes increased	0.5	0.2

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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No prospective efficacy trials have been performed. Immunogenicity of IXIARO was studied in approximately 3,119 healthy adult subjects included in seven randomized, controlled and ~~four~~ five uncontrolled Phase 3 trials and in approximately 550 healthy children included in ~~one~~ two randomized, controlled and ~~one~~ two uncontrolled Phase 3 clinical trials.

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Antibody persistence after booster immunisation (adults)

In an uncontrolled, open-label extension to the booster study described above, 67 subjects were followed up for determination of JEV neutralizing antibody titres at approximately 6 years after a booster dose. 96% of subjects (64/67) still had protective antibody levels ($PRNT_{50}$≥1:10), with a GMT of 148 (95%CI: 107; 207). Mathematical modelling was applied to project the average duration of protection. Based on this model, it is estimated that average duration of protection will be 14 years and 75% of vaccinees will retain protective antibody levels ($PRNT_{50}$≥1:10) for 10 years. A second booster should therefore be given 10 years after the first booster dose, administered 1 year after the primary immunization, prior to potential exposure to JEV.

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Antibody persistence and booster dose in children and adolescents from a JEV-endemic country

The persistence of JEV neutralizing antibodies after primary immunisation and safety and immunogenicity of an IXIARO booster dose 12 months after primary immunization were evaluated in a randomized, controlled, open-label clinical trial conducted in the Philippines, where JEV is endemic (300 children, mean age 5.3 years, range 1.2 - 17.3 years). 150 children were followed-up for three years without booster, additional 150 children received a booster after 1 year (0.25 ml if aged <3 years at time of the booster, 0.5 ml if aged 3 years and above) and were followed-up for further two years. Seroprotection rate (SPR) defined as neutralizing antibody titer ≥1:10 and geometric mean titers (GMT) are presented in Table 11. The booster dose led to a pronounced increase in GMTs and seroprotection rate remained at 100% two years after the booster.

Table 11: Seroprotection Rates and Geometric Mean Titers with and without a booster of IXIARO at Month 12, 13, 24 and 36, Intent To Treat Population

	Without Booster N = 150	Booster dose 12 months after primary immunization N = 149	
Time point after primary immunization		0.25 mL Booster Dose N=81	0.5 mL Booster Dose N=67
Seroprotection Rate % (n/N)			
Month 12	89.9 (134/149)	97.5 (79/81)	89.6 (60/67)
Month 13	n.a.	100 (81/81)	100.0 (67/67)
Month 24	89.0 (130/146)	100 (80/80)	100.0 (67/67)
Month 36	90.1 (128/142)	100.0 (76/76)	100.0 (67/67)
Geometric Mean Titer			
Month 12	46	67	40
Month 13	n.a.	2911	1366
Month 24	50	572	302
Month 36	59	427	280

n.a. = not available

Immunogenicity and safety in children and adolescents from non-endemic countries

The safety and immunogenicity of IXIARO was evaluated in ~~an interim analysis of an ongoing,~~ uncontrolled, open-label clinical trial conducted in the United States, Europe and Australia in healthy male and female subjects with planned travel to JEV-endemic areas. Children and adolescents aged ≥ 3 to < 18 years received two vaccine doses of 0.5ml and children aged ≥ 2 months to < 3 years received two vaccine doses of 0.25ml on Day 0 and Day 28 by

intramuscular injection. ~~An interim analysis was carried out on immunogenicity~~ Immunogenicity data were evaluated in 64 ~~for 54~~ subjects. The SCRs and GMTs are displayed in Table 12.

Table 12: Seroconversion rates and geometric mean titer of JEV neutralizing antibody by vaccine dose and age group. Intent-to-treat Population

	IXIARO Dose	Time Point	SCR n / N	GMT	95% CI
Age Group ≥2 months to <3 years	0.25 ml	Day 56	100% 5/5	216.2	106.0; 441.0
		Month 7	100% 2/2	48.0	0.0; 3214485.7
Age Group ≥3 to <18 years	0.5 ml	Day 56	100% ~~46/46~~ 57/57	~~332.1~~ 340.7	~~251.2; 439.0~~ 269.8; 430.3
		Month 7	~~100%~~ ~~16/16~~ 90.6% 29/32	~~84.0~~ 57.1	~~56.3; 125.4~~ 38.4; 84.9

Antibody persistence in children and adolescents from non-endemic countries

Antibody persistence was evaluated for three years after the primary vaccination with IXIARO in an uncontrolled, open-label follow-up clinical trial conducted in the United States, Europe and Australia. Long-term immunogenicity data were evaluated in 23 children, mean age 14.3 years, range 3 - 18 years). The SPRs and GMTs are displayed in Table 13.

Table 13: Seroprotection rates and geometric mean titer of JEV neutralizing antibody by vaccine dose and age group. Intent-to-treat Population

	Seroprotection Rate (Rate of subjects with $PRNT_{50}$≥1:10) % (n/N)		Geometric Mean Titer (plaque reduction neutralization test) GMT [95%CI]	
	After 0.25 mL Dose Primary Immunization	After 0.5 mL Dose Primary Immunization	After 0.25 mL Dose Primary Immunization	After 0.5 mL Dose Primary Immunization
Month 12	0% (0/0)	89.5% (17/19)	-	48 [28; 80]
Month 24	100% (1/1)	90.9% (20/22)	193 [n.a.]	75 [46; 124]
Month 36	100% (1/1)	88.9% (16/18)	136 [n.a.]	61 [35; 106]

n.a. 95% Confidence Interval could not be established (single-subject data)

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Abbreviations: JEV - Japanese encephalitis virus; SCR - seroconversion rate; GMT - geometric mean titers; PRNT - Plaque Reduction Neutralization Test; SPR - Seroprotection rate.

העלון לרופא המעודכן נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות: https://www.old.health.gov.il/units/pharmacy/trufot/index.asp, וניתן לקבלו מודפס ע"י פניה לבעל הרישום, חברת קמהדע בע"מ (טל' 08-9406472).

בברכה,
פנינה נודל,
רוקחת ממונה

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