DENGVAXIA

Dengue tetravalent vaccine (live, attenuated)

Powder and solvent for suspension for injection

COMPOSITION

After reconstitution, one dose (0.5 mL) contains:

CYD dengue virus serotype 1*.....4.8 - 6.0 log_{10} $CCID_{50}$/dose**
CYD dengue virus serotype 2*.....4.8 - 6.0 log_{10} $CCID_{50}$/dose**
CYD dengue virus serotype 3*.....4.8 - 6.0 log_{10} $CCID_{50}$/dose**
CYD dengue virus serotype 4*.....4.8 - 6.0 log_{10} $CCID_{50}$/dose**
* Produced in serum-free Vero cells by recombinant DNA technology
** $CCID_{50}$: 50% Cell Culture Infectious Dose.

Excipients with known effect: (see section Special Warnings and Precautions)
Phenylalanine……41 micrograms
Sorbitol…….……9.38 milligrams

List of excipients:
Powder:
Essential amino acids including L-Phenylalanine, Non-essential amino acids, L-Arginine hydrochloride, Sucrose. D-Trehalose dehydrate, D-Sorbitol. Trometamol, Urea, Hydrochloric acid and Sodium hydroxide for pH adjustment

Solvent for reconstitution:
Sodium chloride, Water for injections

No adjuvants and no preservatives are added.

DESCRIPTION

Prior to reconstitution, the vaccine is a white, homogenous, freeze-dried powder with possible retraction at the base, and may form a ring-shaped cake.

The solvent is a clear, colorless liquid.

THERAPEUTIC INDICATION

Dengvaxia is indicated for reducing the risk of the event and severity of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 through 16 years of age living in endemic areas who have previously been infected with dengue virus (seropositive).

POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Primary vaccination
The primary vaccination schedule consists of 3 injections of one reconstituted dose (0.5 mL) to be administered at 6-month intervals.

If flexibility in the vaccination schedule is necessary, a time window of +/- 20 days is acceptable (see Section Pharmacodynamic properties).

Dengvaxia should not be administered in individuals less than 9 years of age.

Booster dose
The need for a booster dose after primary vaccination with Dengvaxia has not been established.

Method of administration

Once the freeze-dried vaccine has been completely reconstituted using the solvent provided, it is administered by subcutaneous (SC) injection. The recommended injection site is the deltoid region.

Precautions to be taken before handling or administering the medicinal product

Do not administer by intravascular injection.
Dengvaxia must not be mixed with any other injectable vaccine(s) or medicinal product(s).

For instructions on reconstitution of Dengvaxia before administration, see Section Special precaution for disposal and other handling.

CONTRAINDICATION

Dengvaxia must not be administered to individuals with a history of severe allergic reaction to any component of Dengvaxia or after prior administration of Dengvaxia or a vaccine containing the same components.

Administration of Dengvaxia must be postponed in individuals suffering from moderate to severe febrile or acute disease.

Dengvaxia must not be administered to individuals with congenital or acquired immune deficiency that impairs cell-mediated immunity, including immunosuppressive therapies such as chemotherapy or high doses of systemic corticosteroids generally given for 2 weeks or more.

Dengvaxia must not be administered to individuals with symptomatic HIV infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function.

Dengvaxia must not be administered to pregnant women.

Dengvaxia must not be administered to breastfeeding women.

SPECIAL WARNINGS AND PRECAUTIONS

As with any vaccine, vaccination with Dengvaxia may not protect 100% of vaccinated individuals. It is recommended to continue personal protection measures against mosquito bites after vaccination.

As a precaution, healthcare professionals should follow-up and appropriately manage any vaccinees with signs and symptoms of dengue fever, with particular attention to dengue warning signs (e.g., high fever, severe abdominal pain or tenderness, persistent vomiting, mucosal bleeding, somnolence and hyperactivity according to WHO guidelines 2009).

In individuals who have not been previously infected by the dengue virus, an increased risk of hospitalization for dengue and clinically severe dengue (predominantly grade 1 or 2 Dengue Hemorrhagic Fever [WHO 1997]) has been observed in the long-term follow up of clinical trials (see Section Undesirable Effects).

Vaccination should only be recommended when the potential benefits outweigh the potential risks (for those living in areas with a high dengue seroprevalence or where epidemiological data indicate a high burden of dengue disease). Healthcare professionals would need to assess the likelihood of prior dengue infection in these individuals before vaccinating. For individuals who have not been previously infected by dengue virus, vaccination should not be recommended. Previous infection by dengue virus can be substantiated through serotesting where available.

For patients receiving treatment with high doses of systemic corticosteroids given for 2 weeks or more (daily receipt of prednisone or equivalent 20 mg or 2 mg/kg body weight is considered as a substantially immunosuppressive dose), it is advisable to wait until immune function has recovered, i.e., for at least 4 weeks after stopping treatment, before administering Dengvaxia.

Vaccination is not recommended for individuals without prior dengue infection, living in non-endemic areas, who travel to endemic areas.

Dengvaxia must not be administered by intravascular injection under any circumstances.

In individuals who have a history of serious or severe reactions within 48 hours after a prior administration of Dengvaxia or of a vaccine containing similar components, the risks and benefits of administering Dengvaxia must be carefully considered.

Before administering any biological, the person responsible for administration must take all precautions to prevent allergic or other reactions. As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in the event of an anaphylactic reaction following administration of the vaccine. Epinephrine (1:1000) and other appropriate agents used to control immediate allergic reactions must be available to treat unexpected events such as anaphylaxis.
Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to injection with a needle. Procedures should be in place to prevent injury from falling and to manage syncopal reactions.

No studies have been performed on the interference of Dengvaxia with laboratory and/or diagnostic tests.

The tip caps of the pre-filled syringes contain a natural rubber latex derivative, which may cause allergic reactions in latex sensitive individuals.

Dengvaxia contains phenylalanine, sodium and sorbitol

Dengvaxia contains 41 micrograms of phenylalanine in each 0.5 ml dose of single dose presentation. Phenylalanine may be harmful for people with phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

Dengvaxia contains less than 1mmol of sodium (23 mg) per 0.5 ml dose, that is to say essentially “sodium-free”.

Dengvaxia contains 9.38 milligrams of sorbitol in each 0.5 ml dose of single dose presentation.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Dengvaxia must not be mixed with any other injectable vaccine(s) or medicinal product(s).

Separate syringes and needles, separate injection sites and preferably separate limbs must be used if any other vaccine(s) or medicinal product(s) is/are concomitantly administered.

Dengvaxia has been evaluated in one clinical study on concomitant administration with Tdap (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed) (688 subjects, 9 to 60 years of age), and in two clinical studies with two HPV vaccines (Human Papillomavirus Vaccine, Recombinant) (528 subjects, 9 to 13 years of age and 480 subjects, 9 to 14 years of age).

There was no evidence of an increased rate of reactogenicity or change in the safety profile of the vaccines when Tdap and HPV vaccines were administered concomitantly with Dengvaxia in any of these studies. Antibody responses to Dengvaxia and Tdap vaccine or HPV vaccine components were not negatively affected by concomitant administration.

For patients receiving treatment with immunoglobulins or blood products containing immunoglobulins, such as blood or plasma, it is advisable to wait for at least 6 weeks, and preferably for 3 months, following the end of treatment before administering Dengvaxia, in order to avoid neutralization of the attenuated viruses contained in the vaccine.

For immunosuppressive therapy or corticosteroid therapy, see Sections Contraindications and Special Warnings and Precautions for Use.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Pregnancy constitutes a contraindication (see Section Contraindications).
Women of childbearing age should avoid becoming pregnant for 4 weeks after receiving any injection of Dengvaxia.
Animal studies did not indicate any direct or indirect harmful effects with respect to reproductive toxicity (see Section Preclinical Safety Data).

Breastfeeding

Dengvaxia is contraindicated during breastfeeding (see Section Contraindications).
It is not known whether this vaccine is excreted into human milk. The effect on breastfed infants of administration of Dengvaxia to their mothers has not been studied.
Animal studies did not indicate any direct or indirect harmful effects with respect to lactation (see Section Preclinical Safety Data).

Fertility

No specific studies have been performed on fertility.
Animal studies did not indicate any harmful effects with respect to female fertility (see Section Preclinical Safety Data).

Effects on ability to drive and use machines

No studies have been performed on the effects of the vaccine on the ability to drive or to use machines.

UNDESIRABLE EFFECTS

Data in subjects 9 years of age or older

Summary of the safety profile

A total of approximately 20,667 subjects 9 through 60 years of age received at least one injection of the final formulation of Dengvaxia according to the claimed vaccination schedule in 13 randomized, observer-blinded, placebo-controlled Phase II to Phase III clinical studies.

The safety profile was assessed in a total of 1547 subjects 18 through 60 years of age and 19,120 subjects 9 through 17 years of age. To support the indication, the safety profile presented below is focused on the pooled analysis of safety data in children and adolescents from 9 years of age, i.e. subjects 9 through 17 years of age. Reactogenicity was assessed in a subset of 3068 out of those 19,120 subjects.

Safety was monitored during the first 28 days following each injection in the reactogenicity subset, and serious adverse events (SAEs), including dengue cases, were collected throughout the studies in all subjects, up to at least 6 months after the last injection of vaccine.

In subjects 9 through 17 years of age, the most frequently reported ARs following any injection of the vaccine were headache, injection site pain, malaise and myalgia.

The ARs were usually mild to moderate in severity and of short duration (0 to 3 days). Onset was typically observed 0 to 3 days after the injection, except for fever which appeared within 14 days after the injection.
Systemic ARs tended to be less frequent after the second and third injections as compared to the first injection.

Tabulated list of adverse reactions

Adverse reactions are listed according to the following frequency categories:
Very common: ≥ 1/10 (≥ 10%)
Common: ≥ 1/100 to < 1/10 (≥ 1% and < 10%)
Uncommon: ≥ 1/1000 to < 1/100 (≥ 0.1% and < 1%)
Rare: ≥ 1/10,000 to < 1/1000 (≥ 0.01% and < 0.1%)
Very Rare: <1/10,000 (≥ 0.01%)
ARs within 28 days after any injection in subjects 9 through 17 years of age are presented in Table 1, based on safety data collected during clinical studies.

Table 1: Adverse Reactions from Clinical Studies – Subjects 9 through 17 years of age

System-organ Class	Very Common (≥ 10%)	Common (≥ 1% and < 10%)	Uncommon (≥ 0.1% and < 1%)	Very Rare (<0.01 %)
Infections and infestations			Upper respiratory tract infection	
Blood and lymphatic tissue disorders				
Immune system disorders				Allergic including anaphylactic reactions *
Nervous system disorders	Headache		Dizziness	
Respiratory, thoracic and mediastinal disorders			Oropharyngeal pain, Cough, Rhinorrhoea	
Gastrointestinal disorders			Nausea	
Skin and subcutaneous tissue disorders			Urticaria, Rash	
Musculoskeletal and connective tissue disorders	Myalgia		Neck pain	
General disorders and administration site conditions	Injection site pain, Malaise, Asthenia, Fever	Injection site reactions (erythema swelling)	Injection site reactions (hematoma, pruritus, induration)	

* Adverse reactions from spontaneous reporting

Hospitalized and/or clinically severe dengue fever in long-term safety follow-up data

In an exploratory analysis of up to 6 years of follow up from the first injection in three efficacy studies, an increased risk of hospitalization for dengue including clinically severe dengue (predominantly Dengue Hemorrhagic Fever grade 1 or 2 [WHO 1997]) has been observed in vaccinees with no previous dengue infection. In subjects 9 years of age or older, it was estimated that during a 5 year follow-up about 5 additional hospitalized dengue cases or 2 additional severe dengue cases per 1000 vaccinees with no previous dengue infection could occur following vaccination. Estimates from the long-term analysis suggest the onset of increased risk was mainly during the 3rd year following the first injection.

This increased risk was not observed in individuals who have been previously infected by dengue virus, where it was estimated that 15 hospitalized dengue cases or 4 severe dengue cases could be prevented per 1000 vaccinees with previous dengue infection during 5 years of follow up from the first injection.

OVERDOSE

No cases of overdose have been reported.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Viral vaccines

ATC code: J07BX

J (ANTIINFECTIVES FOR SYSTEMIC USE) 07 (VACCINES) B (VIRAL VACCINES) X (Other viral vaccines)

Mechanism of action

The vaccine contains live attenuated viruses. Following administration, the viruses replicate locally and elicit neutralizing antibodies and cell-mediated immune responses against the four dengue virus serotypes.

Immunogenicity

Immunogenicity data were collected in a total of approximately 3104 subjects 9 through 45 years of age from endemic areas who received at least one injection of the final formulation of the vaccine according to the claimed vaccination schedule in 10 randomized, observer-blinded, placebo-controlled Phase II to Phase III clinical studies. Most of the subjects were 9 through 17 years of age (n= 2810).

The immunogenicity data presented correspond to the neutralizing antibody titers for each serotype as measured with the plaque reduction neutralization test (PRNT). The results are presented as geometric mean titers (GMTs), expressed in reciprocal dilutions (1/dil), measured at baseline and 28 days after the third injection of the vaccine.

GMT data on subjects 18 through 45 years of age included in Phase II safety and immunogenicity studies conducted in endemic areas (CYD22, CYD28 and CYD47) and on subjects 9 through 17 years of age included in the 3 efficacy studies (Phase IIb efficacy study, CYD23, and the two large-scale Phase III efficacy studies, CYD14 and CYD15) are presented by study and region in the Dengue Group and in the Placebo Group in Table 2 (serotypes 1 and 2) and Table 3 (serotypes 3 and 4).

Table 2: Dengue immunogenicity data pre-injection 1 and 28 days post-injection 3 - GMTs of antibodies against serotype 1 and 2 (1/dil) - Dengue PRNT – Subjects 9 through 45 years of age in endemic areas

			Dengue Group					Placebo Group				
			Serotype 1		Serotype 2			Serotype 1		Serotype 2		
Age group	**Region**	**Study**	**N**	**Pre-injection 1 GMT (95% CI)**	**Post-injection 3 GMT (95% CI)**	**N**	**Pre-injection 1 GMT (95% CI)**	**Post-injection 3 GMT (95% CI)**	**N**	**Pre-injection 1 GMT (95% CI)**	**Post-injection 3 GMT (95% CI)**	**N**	**Pre-injection 1 GMT (95% CI)**	**Post-injection 3 GMT (95% CI)**
Subjects 18 through 45 years of age	**Endemic Asia Pacific**	**CYD22**	20	327 (148; 725)	695 (335; 1443)	20	350 (168; 730)	825 (493; 1383)	10	93.5 (22.3; 393)	174 (27.4; 393)	10	200 (70.0; 571)	240 (74.9; 770)
		CYD28	148	15.8 (11.7; 21.5)	48.7 (33.6; 70.4)	148	16.9 (12.3; 23.1)	66.9 (47.9; 93.5)	51	19.2 (10.9; 33.9)	16.2 (9.77; 27.0)	51	21.0 (11.5; 38.2)	15.2 (8.61; 27.0)
		CYD47	126	184 (127; 268)	461 (340; 625)	126	204 (141; 294)	484 (370; 634)	61	234 (133; 409)	268 (164; 438)	61	243 (147; 403)	258 (163; 410)
Subjects 9 through 17 years of age	**Endemic Asia Pacific**	**CYD14**	615	79.5 (65.9; 96.0)	255 (217; 299)	615	133 (111; 159)	530 (469; 600)	311	103 (78.0; 135)	95.6 (73.0; 125)	311	152 (117; 197)	159 (124; 203)
		CYD23	73	98.8 (54.9; 178)	276 (162; 471)	73	123 (69.4; 217)	490 (333; 721)	30	39.8 (17.6; 90.2)	48.0 (21.6; 107)	30	65.0 (27.8; 152)	95.7 (35.6; 257)
	Endemic Latin America	**CYD15**	1301	128 (112; 145)	395 (353; 441)	1301	138 (123; 156)	574 (528; 624)	643	119 (98.7; 142)	121 (101; 145)	643	115 (97.2; 136)	129 (109; 152)

The lower limit of quantification for dengue neutralizing antibodies is 10 (1/dil).

Endemic areas are defined as areas where the disease has been continuously present in the native population with documented outbreaks or epidemics.

CYD22: Vietnam; CYD28: Singapore; CYD47: India; CYD14: Indonesia, Malaysia, the Philippines, Thailand, Vietnam; CYD23: Thailand; CYD15: Brazil, Colombia, Honduras, Mexico, Puerto Rico.

Table 3: Dengue immunogenicity data pre-injection 1 and 28 days post-injection 3 - GMTs of antibodies against serotype 3 and 4 (1/dil) - Dengue PRNT – Subjects 9 through 45 years of age in endemic areas

			Dengue Group						Placebo Group					
			Serotype 3			Serotype 4			Serotype 3			Serotype 4		
Age group	**Region**	**Study**	**N**	**Pre-injection 1 GM (95% CI)**	**Post-injection 3 GM (95% CI)**	**N**	**Pre-injection 1 GM (95% CI)**	**Post-injection 3 GM (95% CI)**	**N**	**Pre-injection 1 GM (95% CI)**	**Post-injection 3 GM (95% CI)**	**N**	**Pre-injection 1 GM (95% CI)**	**Post-injection 3 GM (95% CI)**
Subjects 18 through 45 years of age	**Endemic Asia Pacific**	**CYD22**	20	160 (87.5; 291)	424 (286; 627)	20	75.0 (35.0; 161)	375 (251; 561)	10	90.6 (25.6; 320)	97.4 (32.1; 295)	10	66.6 (17.3; 257)	110 (27.6; 441)
		CYD28	148	14.5 (11.2; 18.7)	88.4 (68.6; 114)	148	10.1 (8.03; 12.7)	122 (96.5; 155)	51	19.4 (11.4; 33.1)	13.3 (8.22; 21.7)	51	11.7 (7.74; 17.6)	10.0 (6.96; 14.4)
		CYD47	126	219 (153; 312)	709 (552; 911)	126	55.4 (41.4; 74.2)	336 (271; 417)	61	216 (131; 354)	268 (168; 426)	61	62.0 (42.0; 91.5)	91.9 (60.8;139)
Subjects 9 through 17 years of age	**Endemic Asia Pacific**	**CYD14**	615	77.0 (64.6; 91.8)	289 (253; 331)	615	46.3 (39.8; 53.8)	201 (181; 223)	311	86.3 (67.9; 110)	79.5 (63.2; 100)	311	54.7 (43.9; 68.0)	44.3 (36.0; 54.6)
		CYD23	73	61.2 (37.5; 100)	457 (320; 651)	73	45.8 (29.1; 72.0)	197 (157; 249)	30	410 (19.2; 87.4)	67.6 (28.9; 158)	30	19.2 (9.48; 39.0)	18.9 (9.53; 37.3)
	Endemic Latin America	**CYD15**	1301	121 (108; 136)	508 (465; 555)	1301	43.6 (39.6; 48.0)	241 (226; 258)	643	114 (95.9; 136)	124 (105; 147)	643	39.0 (33.9; 44.7)	44.3 (38.6; 50.8)

The lower limit of quantification for dengue neutralizing antibodies is 10 (1/dil).

Endemic areas are defined as areas where the disease has been continuously present in the native population with documented outbreaks or epidemics.

CYD22: Vietnam; CYD28: Singapore; CYD47: India; CYD14: Indonesia, Malaysia, the Philippines, Thailand, Vietnam; CYD23: Thailand; CYD15: Brazil, Colombia, Honduras, Mexico, Puerto Rico

In all age groups in all studies, an increase in GMTs was observed for each of the 4 serotypes 28 days after the third injection as compared to baseline, regardless of the region, i.e., Asia Pacific or Latin America.

Differences in GMTs 28 days after the third injection were observed depending on dengue immune status[a] before the first injection, the age and the region. Overall:

- The higher the GMTs before the first injection, the higher the GMTs 28 days after the third injection;
- GMTs 28 days after the third injection were higher in subjects with neutralizing antibodies against dengue virus before the first injection compared to subjects with no detectable neutralizing antibodies against dengue virus before the first injection;
- Dengue immune status before the first injection is a confounding factor of age: the older the subject, the higher the GMTs before the first injection and the higher the GMTs 28 days after the third injection, i.e., the immune response in terms of GMTs 28 days after the third injection increases with age.

Data on *long-term persistence of antibodies*

In subjects 9 years of age and older in endemic areas, a decrease in the GMTs against all 4 serotypes was observed one year after the third injection and then a trend toward stabilization was observed in the subsequent years. The decrease in GMTs was variable depending on age and the dengue immune status of subjects before the first injection. Long-term GMTs for each serotype remained higher than GMTs before the first injection.

Efficacy:

The efficacy of Dengvaxia was assessed in 3 randomized, observer-blinded, placebo-controlled efficacy studies: one supportive Phase IIb efficacy study (CYD23), and 2 pivotal large-scale Phase III efficacy studies conducted in 5 countries each, CYD14 in Asia and CYD15 in Latin America.

In the 2 pivotal Phase III studies, efficacy was assessed in a total of 17,230 subjects 9 through 16 years of age who received at least one injection of the vaccine: 3316 subjects 9 through 14 years of age in CYD14 and the entire study population in CYD15, i.e., 13,914 subjects 9 through 16 years of age. A time window of +/- 20 days was applied for the second and third injections. More than 70% of subjects were dengue immune at baseline.

In subjects 9 through 16 years of age, the efficacy of the vaccine against symptomatic virologically confirmed dengue (VCD) cases due to any and each of the 4 serotypes was demonstrated in both studies, CYD14 and CYD15, and in the meta-analysis. The assessment period extended from the first injection to the end of the active phase, i.e. over the 25-month period after the first injection.

The efficacy of Dengvaxia against severe VCD cases and against hospitalized VCD cases (i.e., hospital admission due to dengue, whatever the severity) were also evaluated. For severe VCD cases, two types of endpoints were considered: clinically severe VCD cases and VCD cases that met WHO criteria for Dengue Hemorrhagic Fever (DHF). Vaccine efficacy was demonstrated for these three endpoints in both studies and in the meta-analysis.

[a] Dengue immune status at baseline (i.e. before the first injection) measured by PRNT is defined as:

- Subjects with quantified (≥ 10 [1/dil], the lower limit of quantitation) neutralizing antibodies against at least one dengue serotype in the baseline sample,
- Subjects without quantified (< the lower limit of quantitation) neutralizing antibodies against any of the 4 dengue serotypes in the baseline sample.

The efficacy results were also analyzed according to covariates, i.e., age at the time of the first injection and dengue immune status before the first injection. In subjects 9 through 16 years of age, no significant effect of age on vaccine efficacy was observed, while a higher efficacy against VCD (any serotype and any severity) was observed in subjects with prior dengue infection (i.e subjects with neutralizing antibodies against any of the 4 dengue serotypes prior vaccination) (81.9% ; 95% CI: 67.2; 90.0) compared to the overall population (65.6% ; 95% CI: 60.7; 69.9) (see Table 4).

The efficacy results in subjects 9 through 16 years of age are presented in Table 4 for each of the two phase III efficacy studies and in the meta-analysis. The results are presented for the entire active phase of 25 months.

Dengue immune status at baseline (i.e. before the first injection) measured by PRNT is define as:

- Subject with qualified (≥ 10 [1/dil], the lower limit of quantitation) neutralizing antibodies against at least one dengue serotype in the baseline sample,
- Subject without qualified (< the lower limit of quantitation) neutralizing antibodies against any of the 4 dengue serotypes in the baseline sample.

Table 4: Vaccine efficacy estimates in subjects 9 through 16 years of age from a meta-analysis of phase III efficacy study data over the 25-month period after the first injection

	CYD14 VE % (95% CI)*	**CYD15 VE % (95% CI)***	**CYD14+CYD15 VE % (95% CI)***
Any serotype	67.8 (57.7; 75.6)	64.7 (58.7; 69.8)	65.6 (60.7; 69.9)
Serotype 1	65.7 (46.6; 78.2)	54.8 (40.2; 65.9)	58.4 (47.7; 66.9)
Serotype 2	36.8 (-10.1; 63.3)	50.2 (31.8; 63.6)	47.1 (31.3; 59.2)
Serotype 3	69.5 (31.9; 87.0)	74.2 (63.9; 81.7)	73.6 (64.4; 80.4)
Serotype 4	87.9 (75.5; 94.6)	80.9 (70.9; 87.7)	83.2 (76.2; 88.2)
Clinically severe VCD cases	90.9 (58.4; 99.0)	95.5 (68.8; 99.9)	93.2 (77.3; 98.0)
DHF meeting any WHO criteria	90.9 (58.4; 99.0)	95.0 (64.9; 99.9)	92.9 (76.1; 97.9)
Hospitalized VCD	81.6 (60.7; 92.0)	80.3 (64.7; 89.5)	80.8 (70.1; 87.7)
VCD any serotype in subjects with neutralizing antibodies against dengue prior vaccination**	79.2 (47.2; 92.7)	83.7 (62.2; 93.7)	81.9 (67.2; 90.0)
VCD any serotype in subjects with no detectable neutralizing antibodies against dengue prior vaccination**	61.6 (-21.1; 88.1)	43.2 (-61.6; 80.0)	52.5 (5.9; 76.1)

* The efficacy of Dengvaxia is considered as significant if the lower bound of the 95% CI is greater than 0.
CI: confidence interval.
**Vaccine efficacy analyses according to dengue immune status and PRNT test before the first injection were performed in the immunogenicity subset of 2 000 subjects per study:

- Subjects with quantified (≥ 10 [1/dil], the lower limit of quantitation) neutralizing antibodies against at least one dengue serotype in the baseline sample,
- Subjects without quantified (< the lower limit of quantitation) neutralizing antibodies against any of the 4 dengue serotypes in the baseline sample.

PHARMACOKINETIC PROPERTIES

No pharmacokinetic studies have been performed on the vaccine.

Preclinical safety data

Non-clinical safety data revealed no special risks for humans based on a repeated-dose toxicity and local tolerance study, a distribution and shedding study, a neurovirulence study and a developmental and reproductive toxicology program.

INCOMPATIBILITES

In the absence of compatibility studies, Dengvaxia must not be mixed with any other injectable vaccine(s) or medicinal product(s).

SHELF-LIFE

Shelf-life: 3 years (36 months)

After reconstitution with the solvent provided, Dengvaxia should be used immediately. However, in-use stability studies have shown that the reconstituted vaccine can be kept for up to 6 hours between 2°C and 8°C (i.e., in a refrigerator) and protected from light.

SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2°C - 8°C). Do not freeze. Store in the outer carton in order to protect from light.

For storage conditions after reconstitution of Dengvaxia, see Section Shelf-life.

PACKAGING PRESENTATION

- [Powder (1 dose) in vial + 0.5 mL of solvent in a pre-filled syringe with 2 separate needles] – pack size of 1. Reg. No. DKI1659703344A1

The tip caps of the pre-filled syringes contain a natural rubber latex derivative.

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Contact with disinfectants is to be avoided since they may inactivate the vaccine viruses.

Separate syringes and needles, separate injection sites and preferably separate limbs must be used if any other vaccine(s) or medicinal product(s) is/are concomitantly administered.

Dengvaxia is reconstituted by transferring all of the solvent (0.4% sodium chloride solution) provided in the blue-labeled pre-filled syringe into the vial of freeze-dried powder with a yellowish green flip-off cap. The pre-filled syringe is fitted with a sterile needle for this transfer. The vial is then gently swirled. After complete dissolution, a 0.5 mL dose of the reconstituted suspension is withdrawn into the same syringe. For injection, the syringe should be fitted with a new sterile needle.

The suspension should be visually inspected prior to administration. After reconstitution, Dengvaxia is a clear, colorless liquid with the possible presence of white to translucent particles (of endogenous nature).

After reconstitution with the solvent provided, Dengvaxia must be used immediately.

Any unused product or waste material should be disposed of, preferably by heat inactivation or incineration, in accordance with local regulations.

MANUFACTURED BY:

SANOFI PASTEUR

27100 Val-De-Reuil, France

RELEASED BY:

SANOFI PASTEUR NVL,

69250 Neuville-Sur-Saone, France

IMPORTED BY

PT AVENTIS PHARMA

Jakarta-Indonesia

HARUS DENGAN RESEP DOKTER

Dengvaxia should not be administered to people who have not previously been infected with dengue virus (seronegative)

Dengvaxia™

Serbuk dan pelarut untuk larutan untuk injeksi
VAKSIN DENGUE TETRAVALEN
(HIDUP,DILEMAHKAN)

Bacalah brosur ini secara hati-hati sebelum anda atau anak anak divaksinasi karena mengandung informasi penting bagi anda.
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- Jika ada pertanyaan lebih lanjut, tanyakanlah pada dokter, apoteker atau perawat.
- Vaksin ini diresepkan untuk anda atau anak anda. Jangan diberikan pada orang lain.
- Jika ada efek samping pada anak anda, bicarakanlah pada dokter, apoteker atau perawat. Hal ini termasuk kemungkinan efek samping apapun yang tidak tertulis pada brosur ini. Lihat pada bagian 4.

Yang tercantum dalam brosur ini:

1. Apa yang dimaksud dengan Dengvaxia™ dan kegunaannya

Dengvaxia™ adalah vaksin yang digunakan untuk mengurangi resiko kejadian dan tingkat keparahan dari penyakit dengue yang disebabkan oleh virus Dengue serotipe 1,2,3 dan 4 pada anak dan remaja berumur 9 sampai 16 tahun yang tinggal di daerah endemis (dimana infeksi dengue sering terjadi) yang sebelumnya telah terinfeksi dengue (seroposi-tive)

Dengvaxia™ mengandung virus dengue serotipe 1,2,3 dan 4 yang telah dilemahkan. Dengvaxia™ bekerja dengan cara memicu pertahanan alami tubuh (sistem kekebalan tubuh) untuk menghasilkan pertahanan tubuh (antibodi) untuk melawan virus penyebab dengue.

Penyakit Dengue merupakan infeksi virus yang menyebar ke manusia melalui gigitan nyamuk Aedes yang terinfeksi. Dengue tidak menyebar secara langsung antar manusia. Namun virus yang bereplikasi di dalam individu yang terinfeksi dapat menyebar ke individu lain melalui gigitan nyamuk selama 4-5 hari (maksimal 12 hari) setelah gejala pertama muncul.

Penyakit Dengue memiliki bermacam-macam gejala termasuk demam, sakit kepala, sakit dibelakang mata, nyeri pada otot dan tulang, mual, muntah, pembengkakan pada kelenjar atau ruam kulit. Gejala umumnya berlangsung selama 2-7 hari. Dengue juga bisa tanpa gejala.

Bagaimanapun, dengue bisa menjadi dengue berat dan berpotensi untuk rawat inap di rumah sakit dan mengakibatkan kematian,walaupun jarang terjadi. Dengue pada tingkat akut dengan demam tinggi disertai gejala berikut ini: nyeri pada perut yang parah, muntah yang menerus, napas cepat, pendarahan yang parah, pendarahan di perut, pendarahan pada gusi, pegal-pegal, gelisah, koma, luka dan gagal organ.

2. Apa yang anda perlu ketahui mengenai Dengvaxia™ sebelum diberikan kepada anak anda atau anda

Untuk memastikan bahwa Dengvaxia™ cocok untuk anda atau anak anda, penting untuk memberitahu dokter, apoteker atau perawat bila salah satu pernyataan dibawah ini terjadi pada anda atau anak anda. Jika ada yang tidak dimengerti, mintalah dokter, apoteker atau perawat untuk menjelaskan.

Jangan memakai Degvaxia™ jika anda atau anak anda:
- Alergi (hipersensitif) pada komponen aktif atau kandungan lain dalam Dengvaxia™ yang tertulis pada bagian 6.
- Mengalami alergi setelah sebelumnya diberi Dengvaxia™. Reaksi alergi ditandai dengan ruam yang gatal, sesak napas dan pembengkakan muka dan lidah.
- Mengalami penyakit dengan demam ringan sampai tinggi atau penyakit akut. Dalam kasus ini maka dokter akan menunda pemberian Dengvaxia™ sampai anda atau anak anda membaik.
- Memiliki sistem kekebalan yang lemah contohnya: akibat kelainan genetik, infeksi HIV atau terapi yang mempengaruhi sistim kekebalan (contoh: kortikosteroid dosis tinggi atau kemoterapi).
- Hamil
- Menyusui

Peringatan dan tindakan pencegahan
Beritahu kepada dokter, apoteker atau perawat sebelum menerima Dengvaxia™ jika anda atau anak anda:
- Belum pernah terinfeksi virus dengue sebelumnya atau jika Anda tidak tahu apakah Anda atau anak Anda pernah terinfeksi virus dengue. Dokter Anda akan dengan hati-hati mempertimbangkan risiko dan manfaat vaksinasi. Jika Anda atau anak Anda tidak pernah terinfeksi virus dengue sebelum vaksinasi, Anda memiliki kemungkinan terjadinya peningkatan resiko rawat inap dan anda memiliki kemungkinan terjadinya resiko dengue berat jika Anda kemudian digigit oleh nyamuk yang terinfeksi dengue.
- Sedang menjalani pengobatan imunosupresif (prednisone atau setara dengan 20 mg atau 2mg/ kg berat badan selama 2 minggu atau lebih). Dokter anda akan menunda pemberian Dengvaxia™ sampai 4 minggu setalah anda berhenti menjalani pengobatan.
- Mengalami masalah kesehatan apapun setelah pemberian jenis vaksin apapun. Dokter anda akan berhati-hati dalam mempertimbangkan manfaat dan kerugian pemberian vaksin.
- Memiliki reaksi alergi terhadap lateks. Tutup ujung *pre-filled syringe* mengandung lateks karet alam yang dapat menyebabkan reaksi alergi.

Sebagaimana vaksi lain, Dengvaxia™ mungkin tidak memberikan perlindungan 100% bagi individu yang telah divaksin. Pemberian Vaksinasi Dengvaxia™ bukan merupakan pengganti perlindungan terhadap gigitan nyamuk. Anda perlu melakukan tindakan pencegahan yang cukup bagi anda dan anak anda untuk mencegah gigitan nyamuk termasuk pemakaian pengusir nyamuk, pakaian yang layak dan kelambu.

Konsultasikan dengan dokter Anda apabila anda atau anak anda telah terinfeksi dengue, dan mengalami gejala berikut: demam tinggi, nyeri perut berat, muntah yang terus menerus, nafas cepat, gusi berdarah, kelelahan, gelisah/tidak nyaman, dan muntah darah.
Pingsan yang disertai jatuh dapat terjadi (umumnya pada remaja) setelah atau terkadang sebelum injeksi menggunakan jarum. Maka dari itu, beritahu dokter, apoteker atau perawat jika anda atau anak anda pingsan sebelum diinjeksi.

Orang yang berpergian
Beritahu dokter jika anda tinggal di daerah dimana infeksi dengue tidak banyak terjadi. Kecuali anda sebelumnya telah terinfeksi virus dengue, vaksinasi tidak direkomendasikan jika anda berencana untuk berpergian ke daerah dimana infeksi dengue sering terjadi.

Anak
Anak dibawah umur 9 tahun sebaiknya tidak divaksin.

Pemakaian obat lain dan Dengvaxia™
Dengvaxia™ mungkin tidak bekerja secara optimal jika digunakan bersama dengan obat yang menekan sistem kekebalan seperti kortikosteroid atau kemoterapi.
Mohon beritahu dokter, apoteker atau perawat jika anak anda sedang atau baru saja diberi vaksin lain atau obat lainnya, termasuk obat yang didapat tanpa resep dokter.

Dengvaxia™ dapat diberikan bersamaan dengan vaksin Difteri, Tetanus, Pertusis dan vaksin Human Papillomavirus rekombinan. Penyuntikan lebih dari satu vaksin pada saat yang sama harus diberikan di tempat suntikan yang berbeda

Kehamilan dan menyusui
Dengvaxia™ sebaiknya tidak diberikan pada wanita hamil atau menyusui, jika anda atau anak anda:
- Berada dalam masa subur, anda perlu mengambil tindakan pencegahan yang diperlukan untuk mencegah kehamilan selama satu bulan setelah anda diberi Dengvaxia™
- Sedang hamil atau menyusui, merasa anda atau anak anda mungkin hamil atau berencana untuk hamil, mintalah pendapat dokter, apoteker atau perawat sebelum menerima Dengvaxia™.

Mengemudi atau menggunakan mesin
Tidak ada data yang tersedia mengenai efek Dengvaxia™ pada kemampuan mengemudi atau menggunakan mesin.

Dengvaxia™ mengandung fenilalanin, natrium, dan sorbitol.
Dengvaxia™ mengandung 41 mikrogram fenilalanin dalam setiap dosis 0,5 mL kemasan single dose. Fenilalanin mungkin berbahaya jika Anda menderita fenilketonuria (PKU), kelainan genetic yang langka di mana fenilalanin menumpuk karena tubuh tidak dapat mengeluarkannya dengan benar.

Dengvaxia™ mengandung kurang dari 1mmol natrium (23 mg) per dosis 0,5 ml, artinya pada dasarnya “bebas natrium”.

Dengvaxia™ mengandung 9,38 miligram sorbitol dalam setiap dosis 0,5 mL kemasan single dose.

3. Cara menggunakan Dengvaxia™
Dengvaxia™ diberikan oleh dokter atau perawat dengan cara disuntikkan kebawah permukaan kulit (jalur subkutan) pada bagian atas lengan.
Anda atau anak anda akan menerima 3 suntikkan masing-masing dengan volume 0,5ml dengan jangka waktu masing-masing 6 bulan. Suntikkan pertama diberikan pada jadwal pilihan anda atau jadwal yang ditentukan, suntikkan kedua diberikan 6 bulan setelah suntikan pertama dan suntikkan ketiga diberikan 6 bulan setelah suntikkan kedua.

Dengvaxia™ sebaiknya diberikan berdasarkan jadwal vaksinasi setempat.

Instruksi pencampuran (rekonstitusi) yang ditujukan bagi pekerja medis dan kesehatan terdapat pada bagian akhir brosur ini.

Jika anda atau anak anda lupa/melewatkan jadwal penyuntikan Dengvaxia™

Jika anda atau anak anda melewatkan jadwal penyuntikkan maka dokter akan menentukan kapan waktu suntikan yang terlewatkan diberikan.

Penting bagi anda atau anak anda untuk mengikuti perintah dokter, apoteker atau perawat mengenai jadwal kunjungan untuk suntikkan berikutnya. Jika anda lupa atau tidak bisa kembali lagi ke dokter, apoteker atau perawat pada waktu yang ditentukan, mintalah saran kepada mereka.

Jika anda memiliki pertanyaan yang lebih lanjut mengenai pemakaian produk ini, tanyalah kepada dokter, apoteker atau perawat.

4. Efek samping yang mungkin terjadi

Seperti obat lainnya, Dengvaxia™ dapat menyebabkan efek samping walaupun tidak semua individu mengalaminya.

Reaksi alergi yang serius

Jika salah satu gejala ini timbul setelah anda meninggalkan tempat di mana anda atau anak anda menerima suntikkan, anda harus SEGERA berkonsutasi dengan dokter anda:

- Kesulitan bernapas.
- Lidah atau bibir membiru.
- Ruam.
- Muka atau tenggorokan membengkak.
- Tekanan darah rendah sehingga pusing atau pingsan.

Jika tanda atau gejala tersebut terjadi, biasanya berkembang secara cepat setelah diberi suntikkan dan terjadi ketika anda atau anak anda masih berada di klinik atau dalam operasi dokter.

Reaksi alergi yang serius sangat jarang terjadi (dapat terjadi pada 1 diantara 10.000 orang) setelah menerima injeksi.

Efek samping lainnya

Efek samping berikut ini dilaporkan pada saat studi klinis pada anak-anak dan remaja (mulai usia 9 tahun dan termasuk usia 17 tahun). Umumnya efek samping terjadi 3 hari setelah vaksin disuntik.

•Sangat umum (dapat terjadi pada lebih dari 1 orang diantara 10)
- Sakit kepala
- Nyeri otot (myalgia)
- Secara umum merasa tidak enak(malaise)
- Merasa lemah (asthenia)
- Nyeri di tempat suntikkan
- Demam

• Umum (dapat terjadi pada 1 diantara 10 orang)
- Reaksi di tempat penyuntikan: kemerahan pada kulit (eritema) dan bengkak.

• Tidak umum (dapat terjadi pada 1 diantara 100 orang)
- Reaksi di tempat penyuntikan : lebam (hematoma) dan gatal (pruritus)
- Infeksi pada bagian atas saluran pernapasan
- Pusing
- Radang tenggorokan (nyeri oropharyngeal)
- Batuk

- Pilek (rhinnorhea)
- Mual
- Ruam
- Nyeri leher
- Ruam yang gatal (urtikaria)

Untuk beberapa orang yang belum pernah terinfeksi dengue sebelum vaksinasi, memiliki kemungkinan terjadinya peningkatan resiko rawat inap dan memiliki kemungkinan terjadinya peningkatan resiko dengue berat jika setelahnya mereka digigit nyamuk yang terinfeksi dengue. Peningkatan resiko ini umumnya terjadi pada tahun ketiga setelah injeksi pertama.

Jika anda mengalami efek samping, bicaralah pada dokter, apoteker atau perawat. Hal ini termasuk kemungkinan efek samping lain yang tidak tertulis dalam brosur ini.

5. Cara penyimpanan Dengvaxia™

Simpan Dengvaxia™ dari jangkauan dan penglihatan anak-anak.
Jangan gunakan Dengvaxia™ setelah tanggal kadaluarsa yang tertulis dalam kotak. Tanggal kadaluarsa mengacu pada hari terakhir bulan tersebut.
Simpan di lemari es (2°C-8°C).
Jangan dibekukan
Simpan vaksin pada bagian luar karton agar terlindung dari cahaya matahari
Jangan membuang obat apapun melalui pembuangan limbah atau limbah rumah tangga.
Tanyakan pada apoteker and acara pembuangan obat yang tidak terpakai lagi. Hal ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

Setelah pencampuran (rekonstitusi), satu dosis (0,5mL)mengandung masing-masing 4,8-6,0 log 10 CCID50* serotipe CYD dengue virus** (1,2,3 dan 4).
*CCID50: 50% dosis sel kultur yang menjangkitkan penyakit
** Diproduksi pada sel vero yang bebas serum melalui teknologi DNA rekombinan.
Kandungan lainnya: asam amino essensial termasuk L-phenylalanin, asam amino non essensial, L-arginin hidroklorida, sukrosa, D-trehalosa dihidrat, D-sorbitol, trometamol, urea, natrium klorida dan air untuk injeksi serta asam klorida dan natrium hidroksida untuk penyesuaian pH.

Tampilan Dengvaxia™ dan kandungan kemasan

Dengvaxia™ merupakan serbuk dan pelarut untuk larutan injeksi. Dengvaxia™ tersedia sebagai serbuk dalam kapsul dosis tunggal dan pelarut dosis tunggal yang sebelumnya telah dimasukkan ke dalam penyuntik (0,5mL) dan dua jarum suntik yang terpisah. Serbuk dan pelarut harus dicampur sebelum dipakai.
Dengvaxia™ tersedia dalam kemasan tunggal.
Serbuk berwarna putih, homogen, serbuk hasil *freeze dried* dengan kemungkinan tarikan pada bagian dasar dengan kemungkinan pembentukan lapisan cincin yang lengket.
Pelarut (0,4% larutan natrium klorida) merupakan larutan jernih dan tidak berwarna.
Setelah pencampuran (rekonstitusi) dengan pelarut yang disediakan, Dengvaxia™ merupakan cairan jernih, tidak berwarna dengan kemungkinan terdapat partikel putih transparan.

Informasi berikut ini ditujukan hanya untuk dokter, apoteker atau perawat:

- Sebelum melakukan tindakan biologis apapun, individu yang bertanggung jawab untuk melakukan tindakan harus mengambil tindakan pencegahan untuk mencegah alergi atau reaksi lainnya. Sebagaimana dengan vaksin lain yang diberikan dengan cara disuntik, tindakan medis yang sesuai dan pengawasan sudah harus tersedia jika terjadi reaksi anaphylactic setelah pemberian Dengvaxia™.

- Epinephrin (1:1000) dan agen lain yang sesuai untuk mengendalikan alergi harus tersedia jika terjadi insiden yang tidak terduga seperti anaphylaxis.
- Dengvaxia™ tidak boleh dicampur dengan produk medis lainnya dalam penyuntik yang sama.
- Dengvaxia™,dalam kondisi apapun, tidak boleh diberikan dengan cara suntikan intravasukar.
- Sinkop (pingsan) dapat terjadi setelah atau bahkan sebelum vaksinasi apapun diberikan sebagai respon psikogenik terhadap suntikkan menggunakan jarum suntik. Perlu tersedia prosedur untuk mencegah kecelakaan karena terjatuh atau untuk mengendalikan reaksi sinkop.
- Penyuntik dan jarum, lokasi penyuntikkan dan bagian tubuh yang terpisah, jika memungkinkan, harus dipakai jika vaksin atau produk medis lain digunakan secara bersamaan.

Dengvaxia™ dicampur (rekonstitusi) dengan cara memindahkan semua pelarut (0,4% larutan natrium klorida) yang disediakan di penyuntik yang sebelumnya sudah terisi yang berlabel biru ke dalam kapsul yang berisi serbuk *freeze-dried* dengan tutup berwarna kuning kehijauan. Penyuntik yang sudah terisi sebelumnya dilengkapi jarum steril untuk pemindahan tersebut. Kapsul kemudian secara pelan-pelan diputar. Setelah peleburan, 0,5ml dari dosis larutan yang sudah dicampurkan (direkonstitusi) diambil dari penyuntik yang sama. Untuk penyuntikkan, penyuntik sebaiknya diisi dengan jarum steril yang baru.
Larutan sebaiknya diperiksa sebelum diberikan. Setelah pencampuran (rekonstitusi), Dengvaxia™ jernih, tidak berwarna dengan kemungkinan timbulnya partikel berwarna putih transparan (bersifat endogenus).
Setelah pencampuran (rekonsitusi) dengan pelarut yang ada, Dengvaxia™ harus langsung digunakan.
Produk yang tidak digunakan atau limbah baiknya dibuang atau, jika memungkinan dengan pemanasan untuk inaktivasi atau pembakaran,sesuai dengan aturan setempat.

PRODUSEN:
Sanofi Pasteur
27100 Val-De-Reuil, France

Dirilis oleh:
Sanofi Pasteur NVL,
69250 Neuville-Sur-Saone, France

PENDAFTAR :
PT AVENTIS PHARMA
Jl. Jend. A. Yani Pulomas,
Jakarta - Indonesia

No. Reg.: DKI1659703344A1

HARUS DENGAN RESEP DOKTER

Dengvaxia tidak boleh diberikan kepada pasien yang belum pernah terinfeksi dengue (seronegative)