

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dengvaxia, powder and solvent for suspension for injection in pre-filled syringe
dengue tetravalent vaccine (live, attenuated)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, one dose (0.5 mL) contains:

Chimeric yellow fever dengue virus serotype 1 (live, attenuated)*	4.5 - 6.0 log ₁₀ CCID ₅₀ /dose**
Chimeric yellow fever dengue virus serotype 2 (live, attenuated)*	4.5 - 6.0 log ₁₀ CCID ₅₀ /dose**
Chimeric yellow fever dengue virus serotype 3 (live, attenuated)*	4.5 - 6.0 log ₁₀ CCID ₅₀ /dose**
Chimeric yellow fever dengue virus serotype 4 (live, attenuated)*	4.5 - 6.0 log ₁₀ CCID ₅₀ /dose**

*Produced in Vero cells by recombinant DNA technology. This product contains genetically modified organisms (GMOs).

**CCID₅₀: 50% Cell Culture Infectious Dose.

Excipients with known effect

One dose (0.5 mL) contains 41 micrograms of phenylalanine and 9.38 milligrams of sorbitol.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection

White, homogenous, freeze-dried powder with possible retraction at the base (ring-shaped cake possible).

The solvent is a clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dengvaxia is indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 6 to 45 years of age with test-confirmed previous dengue infection (see sections 4.2, 4.4 and 4.8).

The use of Dengvaxia should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Children and adults 6 to 45 years of age

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

Booster dose

The added value of and appropriate timing for booster dose(s) have not been established. Current available data are included in section 5.1.

Paediatric population aged less than 6 years

The safety and efficacy of Dengvaxia in children less than 6 years of age have not been established. Dengvaxia should not be used in children less than 6 years of age (see sections 4.4 and 4.8).

Method of administration

Immunisation should be carried out by subcutaneous injection preferably in the upper arm in the region of deltoid.

Do not administer by intravascular injection.

For instructions on reconstitution of Dengvaxia before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, to any of the excipients listed in section 6.1, or after prior administration of Dengvaxia or a vaccine containing the same components.

Individuals with congenital or acquired cell-mediated immune deficiency, including immunosuppressive therapies such as chemotherapy or high doses of systemic corticosteroids (e.g. 20mg or 2mg/kg of prednisone for 2 weeks or more) within 4 weeks prior to vaccination.

Individuals with symptomatic HIV infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function.

Pregnant women (see section 4.6).

Breast-feeding women (see section 4.6).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

Appropriate medical treatment and supervision must always be readily available in the event of an anaphylactic reaction following administration of the vaccine.

Latex

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

Intercurrent illness

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

Syncope

Syncope 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.

Prior dengue infection pre-vaccination screening

Individuals who have not been previously infected by dengue virus should not be vaccinated because of an increased risk of hospitalisation for dengue and clinically severe dengue observed during the long-term follow up of the clinical studies in vaccinated individuals not previously infected (see section 4.8).

In the absence of documented prior dengue virus infection, previous infection must be confirmed by a test before vaccination. To avoid vaccination of false positives, only test methods with adequate performance in terms of specificity and cross-reactivity based on the local disease epidemiology should be used in accordance with official recommendations.

In non-endemic areas or low transmission settings, the use of the vaccine should be restricted to individuals who have high probability of future exposure to dengue.

The lower the proportion of true seropositive individuals, the higher the risk of false seropositives with any test used to determine dengue serostatus. Thus, pre-vaccination testing and vaccination should be limited to individuals with high probability of past dengue infection (e.g. individuals who lived before or had recurrent stay in endemic areas). The objective is to minimise the risk of a false positive test.

Special populations

Women of childbearing potential

Women of childbearing potential have to use effective contraception during at least one month after each dose (see section 4.6).

Travellers

There are no clinical data to support vaccination of individuals living in non-endemic areas with low probability of past dengue infection and who only occasionally travel to endemic areas, therefore vaccination of these individuals is not recommended.

Protection

A protective immune response with Dengvaxia may not be elicited in all vaccinees. It is recommended to continue personal protection measures against mosquito bites after vaccination.

Dengvaxia contains phenylalanine and sodium

Dengvaxia contains 41 micrograms of phenylalanine in each 0.5 ml dose. 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”.

4.5 Interaction with other medicinal products and other forms of interaction

Vaccine-drug interaction

For patients receiving treatment with immunoglobulins or blood products containing immunoglobulins, such as blood or plasma, it is recommended 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.

Dengvaxia should not be administered to subjects receiving immunosuppressive therapies such as chemotherapy or high doses of systemic corticosteroids within 4 weeks prior to vaccination (see section 4.3).

Vaccine-vaccine interaction

Dengvaxia has been evaluated in one clinical study on concomitant administration with Tdap (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed) (629 dengue seropositive subjects at baseline, 9 to 60 years of age). The non-inferiority of the humoral immune response to all Tdap antigens elicited by the Tdap booster dose concomitantly administered with the first dose of Dengvaxia compared to sequential administration was achieved, when measured 28 days after Tdap booster dose in dengue seropositive subjects. In dengue seropositive subjects, the first dose of Dengvaxia induced a similar immune response (in terms of geometric mean titres [GMTs] and seropositivity rates) against all 4 dengue serotypes in both concomitant and sequential administration groups.

Dengvaxia has been evaluated in two clinical studies with bivalent and quadrivalent HPV vaccines (Human Papillomavirus Vaccine, Recombinant) (305 dengue seropositive subjects at baseline, 9 to 14 years of age and 197 dengue seropositive subjects at baseline, 9 to 13 years of age). The non-inferiority of the humoral immune response to bivalent and quadrivalent HPV vaccines / Dengvaxia at 28 days after the last injection could not be assessed because the number of evaluable subjects was limited. Immunogenicity analyses in the concomitant administration group and in the sequential administration group were only descriptive.

Bivalent HPV vaccine showed similar GMTs in both concomitant and sequential administration groups and GMT ratios between groups (concomitant/sequential administration) were near to 1 for both HPV-16 and HPV-18. The GMT ratios between groups (concomitant/sequential administration) were close to 1 for all 4 dengue serotypes.

For the quadrivalent HPV, GMT ratios between groups (concomitant/sequential administration) were close to 1 for HPV-6, and around 0.80 for HPV-11, HPV-16, and HPV-18. The GMTs ratios between groups (concomitant/sequential administration) were close to 1 for serotypes 1 and 4, and close to 0.80 for serotypes 2 and 3.

The clinical relevance of these observations is not known.

There was no evidence of an increased rate of reactogenicity or change in the safety profile of the vaccines when Tdap or HPV vaccines were administered concomitantly with Dengvaxia in any of these studies.

If Dengvaxia is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

As with other live attenuated vaccines, women of childbearing potential have to use effective contraception during at least one month after each dose.

Pregnancy

Animal studies did not indicate any direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

There is limited amount of data from the use of Dengvaxia in pregnant women. These data are not sufficient to conclude on the absence of potential effects of Dengvaxia on pregnancy, embryo-foetal development, parturition and post-natal development.

Dengvaxia is a live attenuated vaccine, therefore Dengvaxia is contraindicated during pregnancy (see section 4.3).

Breast-feeding

Animal studies did not indicate any direct or indirect harmful effects with respect to lactation.

There is very limited experience on dengue virus excretion via breast milk.

Also, considering that Dengvaxia is a live attenuated vaccine and that there is very limited experience from post marketing data with Dengvaxia in breast-feeding women, the vaccine is contraindicated during lactation (see section 4.3).

Fertility

No specific studies have been performed on fertility.

Animal studies did not indicate any harmful effects with respect to female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Dengvaxia has minor influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported reactions were headache (51%), injection site pain (49%), malaise (41%), myalgia (41%), asthenia (32%), and fever (14%).

Adverse reactions occurred within 3 days following vaccination except fever which appears within 14 days after the injection. The adverse reactions were of short duration (0 to 3 days).

Systemic adverse reactions tended to be less frequent after the second and third injections of Dengvaxia as compared to the first injection.

Overall, the same adverse reactions but at lower frequencies were observed in dengue seropositive subjects.

Tabulated list of adverse reactions

Adverse reactions are listed according to the following frequency categories:

Very common: $\geq 1/10$

Common: $\geq 1/100$ to $< 1/10$

Uncommon: $\geq 1/1000$ to $< 1/100$

Rare: $\geq 1/10\ 000$ to $< 1/1000$

Very rare: ($< 1/10\ 000$)

The safety profile presented in **Table 1** is based on a pooled analysis from selected clinical studies and commercial use.

Table 1: Adverse Reactions from clinical studies and post marketing surveillance

System Organ Class	Children and Adolescents	Adults
Adverse Reactions Experienced	6-17 years	18-45 years
	Frequency	Frequency
Infections and infestations		
Upper respiratory tract infection	Uncommon	
Nasopharyngitis	Rare	Uncommon
Blood and lymphatic tissue disorders		
Lymphadenopathy	None ⁺	Uncommon
Immune system disorders		
Allergic including anaphylactic reactions*	Very rare	
Nervous system disorders		
Headache	Very common	
Dizziness	Rare	Uncommon
Respiratory, thoracic and mediastinal disorders		
Cough	Rare	Uncommon
Oropharyngeal pain	Rare	Uncommon
Rhinorrhoea	Rare	None ⁺
Gastrointestinal disorders		
Vomiting	Uncommon	
Nausea	Rare	Uncommon
Dry mouth	None ⁺	Uncommon
Skin and subcutaneous tissue disorders		
Rash	Rare	Uncommon
Urticaria	Rare	None ⁺
Musculoskeletal and connective tissue disorders		
Myalgia	Very common	
Neck pain	Rare	Uncommon
Arthralgia	None ⁺	Uncommon
General disorders and administration site conditions		
Malaise	Very common	
Asthenia	Very common	
Fever	Very common	Common
Chills	Rare	Uncommon
Fatigue	None ⁺	Uncommon
Injection site pain	Very common	
Injection site erythema	Very common	Common
Injection site swelling	Common	
Injection site pruritus	Uncommon	Common
Injection site induration	Uncommon	
Injection site haemorrhage	Uncommon	Rare

System Organ Class Adverse Reactions Experienced	Children and Adolescents 6-17 years	Adults 18-45 years
	Frequency	Frequency
Injection site haematoma	Uncommon	Common
Injection site warmth	None ⁺	Uncommon

* Adverse reactions from spontaneous reporting.

⁺ Not observed in this population

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

In an exploratory analysis of the long-term follow up from the first injection in three efficacy studies, an increased risk of hospitalisation for dengue including clinically severe dengue (predominantly Dengue Haemorrhagic Fever grade 1 or 2 [WHO 1997]) has been observed in vaccinees with no previous dengue infection. Data obtained in the pivotal clinical studies show that over a period of 6 years, in subjects with no previous dengue infection, the risk of severe dengue is increased in subjects 6 to 16 years of age vaccinated with Dengvaxia as compared to non-vaccinated subjects in the same age group. 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 (refer to Section 5.1).

Paediatric population

Paediatric data in subjects 6 to 17 years of age

In paediatric population, fever and injection site erythema have been observed with a higher frequency (very common) than in adults (common).

Urticaria (rare) was only reported in subjects 6 to 17 years of age.

Paediatric data in subjects below 6 years of age, i.e., outside the age indication

The reactogenicity subset in subjects below 6 years of age includes 2192 subjects as follows: 1287 subjects below 2 years of age and 905 subjects between 2 and 5 years of age.

In subjects 2 to 5 years of age, as compared to subjects above 6 years of age, injection site swelling was more frequently reported (frequency: very common), and additional adverse reactions were reported (frequency: uncommon): rash maculo-papular and decreased appetite.

In subjects 2 to 5 years of age, with no previous dengue infection, long-term safety follow-up data showed an increased risk of dengue disease requiring hospitalisation including clinically severe dengue in vaccinated subjects as compared to non-vaccinated subjects (see section 4.4).

In subjects below 2 years of age, the most frequently reported adverse reactions following any injection of Dengvaxia were fever, irritability, appetite lost, abnormal crying and injection site tenderness.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

No cases of overdose have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, Viral vaccines, ATC code: J07BX04

Mechanism of action

Dengvaxia 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.

Clinical efficacy

The clinical efficacy of Dengvaxia was assessed in 3 studies: one supportive Phase IIb efficacy study (CYD23) in Thailand, and 2 pivotal large-scale Phase III efficacy studies, CYD14 in Asia (Indonesia, Malaysia, the Philippines, Thailand, Vietnam) and CYD15 in Latin America (Brazil, Colombia, Honduras, Mexico, Puerto Rico).

In the Phase IIb study, a total of 4002 subjects aged 4 to 11 years were randomised to receive Dengvaxia or a control, regardless of previous dengue infection. Of these subjects 3285 subjects were 6 to 11 years of age (2184 in vaccine group and 1101 in Control Group).

In the two pivotal Phase III studies (CYD14 and CYD15), a total of approximately 31000 subjects aged 2 to 16 years were randomised to receive either Dengvaxia or placebo, regardless of previous dengue infection. Of these subjects, 19 107 subjects who received Dengvaxia (5193 subjects in CYD14 and 13914 in CYD15) and 9538 subjects who received placebo (2598 in CYD14 and 6940 in CYD15) were 6 to 16 years of age.

At the start of the CYD14 and CYD15 studies, dengue seroprevalence for the overall population at the study sites ranged from 52.8%-81.1% in CYD14 (Asia-Pacific) and 55.7%-92.7% in CYD15 (Latin America).

The efficacy was assessed during an Active Phase of 25 months, in which surveillance was designed to maximize the detection of all symptomatic virologically-confirmed dengue (VCD) cases regardless of the severity. The active detection of symptomatic dengue cases started on the day of the first injection and lasted until 13 months after the third injection.

For the primary endpoint, the incidence of symptomatic VCD cases occurring during the 12-month period from 28 days after the third injection was compared between the vaccine and the Control Group.

Exploratory vaccine efficacy analyses according to dengue serostatus measured by plaque reduction neutralization test (PRNT50) at baseline (before the first injection) were performed in the immunogenicity subset of 2000 subjects each in CYD14 and CYD15 and 300 subjects in CYD23. Of the 2580 subjects 6 to 16 years old in this subset (approximately 80%) who were dengue seropositive at baseline, 1729 subjects received the vaccine (656 subjects in CYD14 and 1073 in CYD15) and 851 subjects received placebo (339 in CYD14 and 512 in CYD15) (see also subsection Immunogenicity).

Clinical efficacy data for subjects 6 to 16 years of age in endemic areas, any serostatus at baseline

The Vaccine Efficacy (VE) results according to the primary endpoint (symptomatic VCD cases occurring during the 25-month period after the first dose) in subjects 6 to 16 years of age (any serostatus at baseline) are shown in **Table 2** for studies CYD14, CYD15 and CYD23.

Table 2: VE against symptomatic VCD cases during the 25-month period after the first dose due to any of the 4 serotypes in subjects 6 to 16 years (any serostatus at baseline).

	CYD14		CYD15		CYD23		Pooled CYD14+CYD15		Pooled* CYD14+CYD15+ CYD23	
	Vaccine group	Control group	Vaccine group	Control group	Vaccine group	Control group	Vaccine group	Control group	Vaccine group	Control group
Cases / person-years	166/10352	220/5039	227/26883	385/13204	62/4336	46/2184	393/37235	605/18243	455/41571	651/20427
VE % (95%CI)	63.3 (54.9 ; 70.2)		64.7 (58.7; 69.8)		32.1 (-1.7; 54.4)		64.2 (59.6; 68.4)		62.0 (57.3; 66.2)	

N: number of subjects per study

Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode in the considered period.

Person-years: sum of time-at-risk (in years) for the subjects during the study period.

CI: confidence interval.

*Pooled results of CYD14, 15 and 23 need to be interpreted cautiously because of differences in the Dengue confirmatory test and acute febrile illness definition between CYD14/15 and CYD23.

In subjects 6 to 16 years of age, the efficacy of Dengvaxia against symptomatic virologically-confirmed dengue (VCD) cases due to any of the 4 serotypes was demonstrated in all three studies, CYD14, CYD15 and CYD23 (see **Table 2**).

Clinical efficacy data for subjects 6 to 16 years of age in endemic areas, dengue seropositive at baseline

VE against symptomatic VCD cases in subjects 6 to 16 years of age

The Vaccine Efficacy (VE) results according to exploratory analysis of symptomatic VCD cases occurring during the 25-month period after the first dose in subjects 6 to 16 years of age, seropositives at baseline are shown in **Table 3** for the immunogenicity subset of studies CYD14, CYD15 and CYD23.

Table 3: VE against symptomatic VCD cases during the 25-month period after the first dose due to any of the 4 serotypes in subjects 6 to 16 years (dengue seropositive at baseline).

	CYD14		CYD15		CYD23		Pooled CYD14+CYD15		Pooled * CYD14+CYD15+ CYD23	
	Vaccine group	Control group	Vaccine group	Control group	Vaccine group	Control group	Vaccine group	Control group	Vaccine group	Control group
Cases / person- years	12/1320	25/671	8/2116	23/994	2/248	5/114	20/3436	48/1665	22/3684	53/1779
VE % (95%CI)	75.6 (49.6; 88.8)		83.7 (62.2; 93.7)		81.6 (-12.6; 98.2)		79.7 (65.7; 87.9)		79.9 (66.9; 87.7)	

N: number of subjects per study

Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode in the considered period.

Person-years: sum of time-at-risk (in years) for the subjects during the study period.

CI: confidence interval.

NC: Not computed (the absence of cases in vaccine and control group does not permit to calculate VE nor CI)

*Pooled results of CYD14, 15 and 23 need to be interpreted cautiously because of differences in the Dengue confirmatory test and acute febrile illness definition between CYD14/15 and CYD23.

The four serotypes contributed to the overall Vaccine Efficacy (VE). Data are limited because baseline immunostatus was initially collected in a limited subset of subjects. VE against symptomatic VCD due to serotype 1 [76.8 (46.1; 90.0)] and to serotype 2 [55.5 (-15.5; 82.8)] tends to be lower compared to serotypes 3 [89.6 (63.7; 97.0)] and serotype 4 [96.5 (73.4; 99.5)] during the 25-month period after the first dose, for subjects 6 to 16 years who are seropositive at baseline (immunogenicity subset of studies CYD14, CYD15 and CYD23).

Efficacy tends to be slightly lower in the 6-8 years of age compared to children 9-16 years of age.

VE against hospitalized and severe VCD cases in subjects 6 to 16 years of age

In subjects 6 to 16 years of age, dengue seropositive at baseline (immunogenicity subset), two clinically severe VCD cases in CYD14 and one in CYD15 were reported during the 25-month period after the first injection in the control group versus none in the vaccine group. Eight hospitalized VCD cases in CYD14 were reported in the control group versus one in the vaccine group and two hospitalized VCD cases in CYD15 were reported in the control group versus none in the vaccine group. These data are inconclusive due to the low number of cases in the immunogenicity subset.

Efficacy was assessed in moderate-high endemic areas. The magnitude of protection may not be extrapolated to other epidemiological situations.

Clinical efficacy data for subjects 17 to 45 years of age in endemic areas

No clinical efficacy study has been done in subjects from 17 to 45 years from endemic areas. The clinical efficacy of the vaccine is based on bridging of immunogenicity data (see below section *Immunogenicity data for subjects 18 to 45 years of age in endemic areas*).

Long-term protection

Limited data suggest a trend for efficacy to decrease over time. During the last 2 years of follow-up (Year 5 and 6) after the initial dose, vaccine efficacy against symptomatic VCD (Immunogenicity Subset, pooled CYD14+CYD15) was 14.6% (95% CI: -74.7; 58.3) in subjects 6 to 16 years with previous dengue infection. Efficacy persistence may vary according to the epidemiological situations.

Immunogenicity

No immune correlate of protection has been established. During clinical development, immunogenicity data were collected in a total of 7262 subjects 9 months to 60 years of age that received at least one injection of the vaccine.

Among these subjects, a total of 3498 subjects 6 to 45 years of age from endemic areas and dengue immune received at least one injection of Dengvaxia. Most of the subjects were 6 to 17 years of age (n=2836).

During clinical development, neutralizing antibody titres for each serotype were measured with the plaque reduction neutralization test (PRNT) and presented as geometric mean titres (GMTs).

In the following Tables the dengue serostatus at baseline (before the first injection), was defined as:

- Dengue seropositivity if the PRNT50 titre ≥ 10 [1/dil] (the lower limit of quantification, LLOQ), against at least one serotype.
- Dengue seronegativity if the PRNT50 titre < the lower limit of quantification against any of the 4 serotypes.

Immunogenicity data for subjects 6 to 8 years of age in endemic areas

GMTs at baseline and 28 days post-dose 3 in subjects 6 to 8 years of age in CYD14 are shown in the Table 5

Table 4: Immunogenicity for dengue seropositive subjects 6 to 8 years of age in CYD14 from endemic areas

Study	N	Serotype 1		Serotype 2		Serotype 3		Serotype 4	
		Pre-dose 1 GMT (95%CI)	Post-dose 3 GMT (95%CI)	Pre-dose 1 GMT (95%CI)	Post-dose 3 GMT (95%CI)	Pre-dose 1 GMT (95%CI)	Post-dose 3 GMT (95%CI)	Pre-dose 1 GMT (95%CI)	Post-dose 3 GMT (95%CI)
CYD14	168	80.8 (57.3; 114)	203 (154; 268)	118 (86.0; 161)	369 (298; 457)	105 (75.5; 145)	316 (244; 411)	48.4 (37.2; 63.0)	175 (145; 211)

N: number of subjects with available antibody titre for the relevant endpoint

Dengue seropositive subjects are subjects with titres above or equal to LLOQ against at least one dengue serotype at baseline

CI: Confidence Interval

CYD14: Indonesia, Malaysia, the Philippines, Thailand, Vietnam.

Immunogenicity data for subjects 9 to 17 years of age in endemic areas

GMTs at baseline and 28 days post-dose 3 in subjects 9 to 16 years of age in CYD14 and CYD15 are shown in the Table 5.

Table 5: Immunogenicity for dengue seropositive subjects 9 to 16 years of age in CYD14 and CYD15 from endemic areas

Study	N	Serotype 1		Serotype 2		Serotype 3		Serotype 4	
		Pre-injection 1 GMT (95%CI)	Post-injection 3 GMT (95%CI)	Pre-injection 1 GMT (95%CI)	Post-injection 3 GMT (95%CI)	Pre-injection 1 GMT (95%CI)	Post-injection 3 GMT (95%CI)	Pre-injection 1 GMT (95%CI)	Post-injection 3 GMT (95%CI)
CYD14	485	167 (138; 202)	437(373; 511)	319 (274; 373)	793(704; 892)	160 (135; 190)	443(387; 507)	83.8 (72.0; 97.6)	272(245; 302)
CYD15	1048	278 (247; 313)	703(634; 781)	306 (277; 338)	860(796; 930)	261 (235; 289)	762(699; 830)	73.3 (66.6; 80.7)	306(286; 328)

N: number of subjects with available antibody titre for the relevant endpoint

Dengue seropositive subjects are subjects with titres above or equal to LLOQ against at least one dengue serotype at baseline

CI: Confidence Interval

CYD14: Indonesia, Malaysia, the Philippines, Thailand, Vietnam.

CYD15: Brazil, Colombia, Honduras, Mexico, Puerto Rico.

Immunogenicity data for subjects 18 to 45 years of age in endemic areas

The immunogenicity of the final formulation of the CYD dengue vaccine in adults aged 18 to 45 years in endemic areas was assessed in 3 studies conducted all in Asia-Pacific (CYD22 in Vietnam, CYD28 in Singapore and CYD47 in India).

GMTs at baseline and 28 days post-dose 3 in subjects 18 to 45 years of age are shown in the Table 6

Table 6: Immunogenicity for dengue seropositive subjects 18 to 45 years of age from endemic areas

Study	N	Serotype 1		Serotype 2		Serotype 3		Serotype 4	
		Pre-injection 1 GMT (95%CI)	Post-injection 3 GMT (95%CI)	Pre-injection 1 GMT (95%CI)	Post-injection 3 GMT (95%CI)	Pre-injection 1 GMT (95%CI)	Post-injection 3 GMT (95%CI)	Pre-injection 1 GMT (95%CI)	Post-injection 3 GMT (95%CI)
CYD22	19	408 (205; 810)	785 (379; 1626)	437 (240; 797)	937 (586; 1499)	192 (117; 313)	482 (357; 651)	86.5 (41.2; 182)	387 (253; 591)
CYD28	66	59.8 (36.8;97.4)	235 (135; 409)	67.1 (40.9; 110)	236 (144; 387)	48.4 (32.9;71.0)	239 (166; 342)	22.1 (14.7;33.4)	211 (155; 287)
CYD47	109	324 (236; 445)	688 (524; 901)	363 (269; 490)	644 (509; 814)	394 (299; 519)	961 (763; 1211)	80.7 (613; 106)	413(331; 516)

N: number of subjects with available antibody titre for the relevant endpoint

Dengue seropositive subjects are subjects with titres above or equal to LLOQ against at least one dengue serotype at baseline

CI: Confidence Interval

CYD28: Low endemic country

CYD22: Vietnam; CYD28: Singapore; CYD47: India;

The bridging of efficacy is based on above available data and overall results. Immunogenicity data available from studies in adults aged 18 to 45 years in endemic regions show that post-injection 3 GMTs against each serotype are generally higher in adults than in children and adolescents in CYD14 and CYD15. Therefore, protection is expected in adults in endemics areas although the actual magnitude of efficacy relative to that observed in children and adolescents is unknown.

Long-term persistence of antibodies

The GMTs persisted post dose 3 up to 5 years in subjects 6 years of age and older in studies CYD14 and CYD15. At year 5 after the third injection, GMTs were still higher to pre-vaccination GMTs despite decrease in the GMTs against all 4 serotypes compared to post-dose 3 GMTs. The GMTs levels depend on age and dengue serostatus at baseline.

The effect of a booster dose was assessed in subjects 9-50 years living in endemic areas after a 3-dose schedule (studies CYD63, CYD64, CYD65). No or modest transient increase of neutralizing Ab titers was observed after the boost. The booster effect was variable across serotypes and studies. Why there

is a lack/limited booster effect with Dengvaxia remains not understood in terms of mechanisms and clinical implications.

5.2 Pharmacokinetic properties

No pharmacokinetic studies have been performed on Dengvaxia.

5.3 Preclinical safety data

Non-clinical safety data revealed no special risks for humans based on a repeated-dose toxicity including assessment of local tolerance, and a developmental and reproductive toxicology program. A neurovirulence study shows that CYD dengue vaccine is not neurotoxic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Essential amino acids including Phenylalanine

Non-essential amino acids

Arginine hydrochloride

Sucrose

Trehalose dihydrate

Sorbitol (E420)

Trometamol

Urea

Hydrochloric acid and sodium hydroxide for pH adjustment

Solvent:

Sodium chloride

Water for injections

6.2 Incompatibilities

Dengvaxia must not be mixed with any other vaccine or medicinal product.

6.3 Shelf life

3 years

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

6.4 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 6.3.

6.5 Nature and contents of container

- Powder (1 dose) in vial (Type-I glass), with a stopper (halobutyl) and a flip-off cap (aluminium, polypropylene) + 0.5 mL of solvent in a pre-filled syringe (Type-I glass), with a plunger stopper (halobutyl) and a tip cap (elastomer) with 2 separate needles.

Pack size of 1 or 10.

- Powder (1 dose) in vial (Type-I glass), with a stopper (halobutyl) and a flip-off cap (aluminium, polypropylene) + 0.5 mL of solvent in pre-filled syringe (Type-I glass), with a plunger stopper (halobutyl) and a tip cap (elastomer).

Pack size of 1 or 10.

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Dengvaxia must be reconstituted prior to administration.

Dengvaxia is reconstituted by transferring all of the solvent (0.4% sodium chloride solution) provided in the blue-labelled pre-filled syringe into the vial of freeze-dried powder with a yellowish green flip-off cap.

1. Attach a sterile needle to the pre-filled syringe for the transfer of the solvent. The needle must be fitted firmly to the syringe, rotating it by a one-quarter turn.
2. Transfer the entire content of the pre-filled syringe into the vial containing the powder.
3. Swirl gently until the powder is completely dissolved.

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

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.

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

Any unused product or waste material should be disposed of in accordance with local regulations.

7. MARKETING AUTHORISATION HOLDER

Sanofi Pasteur
14 Espace Henry Vallée
69007 Lyon
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1338/001

EU/1/18/1338/002

EU/1/18/1338/003

EU/1/18/1338/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 December 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

Dengvaxia, powder and solvent for suspension for injection in multidose containers
dengue tetravalent vaccine (live, attenuated)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, one dose (0.5 mL) contains:

Chimeric yellow fever dengue virus serotype 1 (live, attenuated)*	4.5 - 6.0 log ₁₀ CCID ₅₀ /dose**
Chimeric yellow fever dengue virus serotype 2 (live, attenuated)*	4.5 - 6.0 log ₁₀ CCID ₅₀ /dose**
Chimeric yellow fever dengue virus serotype 3 (live, attenuated)*	4.5 - 6.0 log ₁₀ CCID ₅₀ /dose**
Chimeric yellow fever dengue virus serotype 4 (live, attenuated)*	4.5 - 6.0 log ₁₀ CCID ₅₀ /dose**

*Produced in Vero cells by recombinant DNA technology. This product contains genetically modified organisms (GMOs).

**CCID₅₀: 50% Cell Culture Infectious Dose.

Excipients with known effect: One dose (0.5 mL) contains 8 micrograms of phenylalanine and 1.76 milligrams of sorbitol.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection

White, homogenous, freeze-dried powder with possible retraction at the base (ring-shaped cake possible).

The solvent is a clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dengvaxia is indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 6 to 45 years of age with test-confirmed previous dengue infection (see sections 4.2, 4.4 and 4.8).

The use of Dengvaxia should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Children and adults 6 to 45 years of age

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

Booster dose

The added value of and appropriate timing for booster dose(s) have not been established. Current available data are included in section 5.1.

Paediatric population aged less than 6 years

The safety and efficacy of Dengvaxia in children less than 6 years of age have not been established. Dengvaxia should not be used in children less than 6 years of age (see sections 4.4 and 4.8).

Method of administration

Immunisation should be carried out by subcutaneous injection preferably in the upper arm in the region of deltoid.

Do not administer by intravascular injection.

For instructions on reconstitution of Dengvaxia before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, to any of the excipients listed in section 6.1, or after prior administration of Dengvaxia or a vaccine containing the same components.

Individuals with congenital or acquired cell-mediated immune deficiency, including immunosuppressive therapies such as chemotherapy or high doses of systemic corticosteroids (e.g. 20mg or 2mg/kg of prednisone for 2 weeks or more) within 4 weeks prior to vaccination.

Individuals with symptomatic HIV infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function.

Pregnant women (see section 4.6).

Breast-feeding women (see section 4.6).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

Appropriate medical treatment and supervision must always be readily available in the event of an anaphylactic reaction following administration of the vaccine.

Intercurrent illness

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

Syncope

Syncope 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.

Prior dengue infection pre-vaccination screening

Individuals who have not been previously infected by dengue virus should not be vaccinated because of an increased risk of hospitalisation for dengue and clinically severe dengue as observed during the long-term follow up of the clinical studies in vaccinated individuals not previously infected (see section 4.8).

In the absence of documented prior dengue virus infection, previous infection must be confirmed by a test before vaccination. To avoid vaccination of false positives, only test methods with adequate performance in terms of specificity and cross-reactivity based on the local disease epidemiology should be used in accordance with official recommendations.

In non-endemic areas or low transmission settings, the use of the vaccine should be restricted to individuals who have high probability of future exposure to dengue.

The lower the proportion of true seropositive individuals, the higher the risk of false seropositives with any test used to determine dengue serostatus. Thus, pre-vaccination testing and vaccination should be limited to individuals with high probability of past dengue infection (e.g. individuals who lived before or had recurrent stay in endemic areas). The objective is to minimise the risk of a false positive test.

Special populations

Women of childbearing potential

Women of childbearing potential have to use effective contraception during at least one month after each dose (see section 4.6).

Travellers

There are no clinical data to support vaccination of individuals living in non-endemic areas with low probability of past dengue infection and who only occasionally travel to endemic areas, therefore vaccination of these individuals is not recommended.

Protection

A protective immune response with Dengvaxia may not be elicited in all vaccinees. It is recommended to continue personal protection measures against mosquito bites after vaccination.

Dengvaxia contains phenylalanine and sodium

Dengvaxia contains 8 micrograms of phenylalanine in each 0.5 ml dose. 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”.

4.5 Interaction with other medicinal products and other forms of interaction

Vaccine-drug interaction

For patients receiving treatment with immunoglobulins or blood products containing immunoglobulins, such as blood or plasma, it is recommended 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.

Dengvaxia should not be administered to subjects receiving immunosuppressive therapies such as chemotherapy or high doses of systemic corticosteroids within 4 weeks prior to vaccination (see section 4.3).

Vaccine-vaccine interaction

Dengvaxia has been evaluated in one clinical study on concomitant administration with Tdap (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed) (629 dengue seropositive subjects at baseline, 9 to 60 years of age). The non-inferiority of the humoral immune response to all Tdap antigens elicited by the Tdap booster dose concomitantly administered with the first dose of Dengvaxia compared to sequential administration was achieved, when measured 28 days after Tdap booster dose in dengue seropositive subjects. In dengue seropositive subjects, the first dose of Dengvaxia induced a similar immune response (in terms of geometric mean titres [GMTs] and seropositivity rates) against all 4 dengue serotypes in both concomitant and sequential administration groups.

Dengvaxia has been evaluated in two clinical studies with bivalent and quadrivalent HPV vaccines (Human Papillomavirus Vaccine, Recombinant) (305 dengue seropositive subjects at baseline, 9 to 14 years of age and 197 dengue seropositive subjects at baseline, 9 to 13 years of age). The non-inferiority of the humoral immune response to bivalent and quadrivalent HPV vaccines / Dengvaxia at 28 days after the last injection could not be assessed because the number of evaluable subjects was limited. Immunogenicity analyses in the concomitant administration group and in the sequential administration group were only descriptive.

Bivalent HPV vaccine showed similar GMTs in both concomitant and sequential administration groups and GMT ratios between groups (concomitant/sequential administration) were near to 1 for both HPV-16 and HPV-18. The GMT ratios between groups (concomitant/sequential administration) were close to 1 for all 4 dengue serotypes.

For the quadrivalent HPV, GMT ratios between groups (concomitant/sequential administration) were close to 1 for HPV-6, and around 0.80 for HPV-11, HPV-16, and HPV-18. The GMTs ratios between groups (concomitant/sequential administration) were close to 1 for serotypes 1 and 4, and close to 0.80 for serotypes 2 and 3.

The clinical relevance of these observations is not known.

There was no evidence of an increased rate of reactogenicity or change in the safety profile of the vaccines when Tdap or HPV vaccines were administered concomitantly with Dengvaxia in any of these studies.

If Dengvaxia is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

As with other live attenuated vaccines, women of childbearing potential have to use effective contraception during at least one month after each dose.

Pregnancy

Animal studies did not indicate any direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

There is limited amount of data from the use of Dengvaxia in pregnant women. These data are not sufficient to conclude on the absence of potential effects of Dengvaxia on pregnancy, embryo-foetal development, parturition and post-natal development.

Dengvaxia is a live attenuated vaccine, therefore Dengvaxia is contraindicated during pregnancy (see section 4.3).

Breast-feeding

Animal studies did not indicate any direct or indirect harmful effects with respect to lactation.

There is very limited experience on dengue virus excretion via breast milk.

Also, considering that Dengvaxia is a live attenuated vaccine and that there is very limited experience from post marketing data with Dengvaxia in breast-feeding women, the vaccine is contraindicated during lactation (see section 4.3).

Fertility

No specific studies have been performed on fertility.

Animal studies did not indicate any harmful effects with respect to female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Dengvaxia has minor influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported reactions were headache (51%), injection site pain (49%), malaise (41%), myalgia (41%), asthenia (32%), and fever (14%).

Adverse reactions occurred within 3 days following vaccination except fever which appears within 14 days after the injection. The adverse reactions were of short duration (0 to 3 days).

Systemic adverse reactions tended to be less frequent after the second and third injections of Dengvaxia as compared to the first injection.

Tabulated list of adverse reactions

Adverse reactions are listed according to the following frequency categories:

Very common: $\geq 1/10$

Common: $\geq 1/100$ to $< 1/10$

Uncommon: $\geq 1/1000$ to $< 1/100$

Rare: $\geq 1/10\ 000$ to $< 1/1000$

Very rare: ($< 1/10\ 000$)

The safety profile presented in **Table 1** is based on a pooled analysis from selected clinical studies and commercial use.

Table 1: Adverse Reactions from clinical studies and post marketing surveillance

System Organ Class	Children and Adolescents	Adults
Adverse Reactions Experienced	6-17 years	18-45 years
	Frequency	Frequency
Infections and infestations		
Upper respiratory tract infection	Uncommon	
Nasopharyngitis	Rare	Uncommon
Blood and lymphatic tissue disorders		
Lymphadenopathy	None ⁺	Uncommon
Immune system disorders		
Allergic including anaphylactic reactions*	Very rare	
Nervous system disorders		
Headache	Very common	
Dizziness	Rare	Uncommon
Respiratory, thoracic and mediastinal disorders		
Cough	Rare	Uncommon
Oropharyngeal pain	Rare	Uncommon
Rhinorrhoea	Rare	None ⁺
Gastrointestinal disorders		
Vomiting	Uncommon	
Nausea	Rare	Uncommon
Dry mouth	None ⁺	Uncommon
Skin and subcutaneous tissue disorders		
Rash	Rare	Uncommon
Urticaria	Rare	None ⁺
Musculoskeletal and connective tissue disorders		
Myalgia	Very common	
Neck pain	Rare	Uncommon
Arthralgia	None ⁺	Uncommon
General disorders and administration site conditions		
Malaise	Very common	
Asthenia	Very common	
Fever	Very common	Common
Chills	Rare	Uncommon
Fatigue	None ⁺	Uncommon
Injection site pain	Very common	
Injection site erythema	Very common	Common
Injection site swelling	Common	
Injection site pruritus	Uncommon	Common
Injection site induration	Uncommon	
Injection site haemorrhage	Uncommon	Rare

System Organ Class Adverse Reactions Experienced	Children and Adolescents 6-17 years	Adults 18-45 years
	Frequency	Frequency
Injection site haematoma	Uncommon	Common
Injection site warmth	None ⁺	Uncommon

* Adverse reactions from spontaneous reporting.

⁺ Not observed in this population

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

In an exploratory analysis of the long-term follow up from the first injection in three efficacy studies, an increased risk of hospitalisation for dengue including clinically severe dengue (predominantly Dengue Haemorrhagic Fever grade 1 or 2 [WHO 1997]) has been observed in vaccinees with no previous dengue infection. Data obtained in the pivotal clinical studies show that over a period of 6 years, in subjects with no previous dengue infection, the risk of severe dengue is increased in subjects 6 to 16 years of age vaccinated with Dengvaxia as compared to non-vaccinated subjects in the same age group. 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 (refer to Section 5.1).

Paediatric population

Paediatric data in subjects 6 to 17 years of age

In paediatric population, fever and injection site erythema have been observed with a higher frequency (very common) than in adults (common).

Urticaria (rare) was only reported in subjects 6 to 17 years of age.

Paediatric data in subjects below 6 years of age, i.e., outside the age indication

The reactogenicity subset in subjects below 6 years of age includes 2192 subjects as follows: 1287 subjects below 2 years of age and 905 subjects between 2 and 5 years of age.

In subjects 2 to 5 years of age, as compared to subjects above 6 years of age, injection site swelling was more frequently reported (frequency: very common), and additional adverse reactions were reported (frequency: uncommon): rash maculo-papular and decreased appetite.

In subjects 2 to 5 years of age, with no previous dengue infection, long-term safety follow-up data showed an increased risk of dengue disease requiring hospitalisation including clinically severe dengue in vaccinated subjects as compared to non-vaccinated subjects (see section 4.4).

In subjects below 2 years of age, the most frequently reported adverse reactions following any injection of Dengvaxia were fever, irritability, appetite lost, abnormal crying and injection site tenderness.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

No cases of overdose have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, Viral vaccines, ATC code: J07BX04

Mechanism of action

Dengvaxia 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.

Clinical efficacy

The clinical efficacy of Dengvaxia was assessed in 3 studies: one supportive Phase IIb efficacy study (CYD23) in Thailand, and 2 pivotal large-scale Phase III efficacy studies, CYD14 in Asia (Indonesia, Malaysia, the Philippines, Thailand, Vietnam) and CYD15 in Latin America (Brazil, Colombia, Honduras, Mexico, Puerto Rico).

In the Phase IIb study, a total of 4002 subjects aged 4 to 11 years were randomised to receive Dengvaxia or a control, regardless of previous dengue infection. Of these subjects 3285 subjects were 6 to 11 years of age (2184 in vaccine group and 1101 in Control Group).

In the two pivotal Phase III studies (CYD14 and CYD15), a total of approximately 31000 subjects aged 2 to 16 years were randomised to receive either Dengvaxia or placebo, regardless of previous dengue infection. Of these subjects, 19 107 subjects who received Dengvaxia (5193 subjects in CYD14 and 13914 in CYD15) and 9538 subjects who received placebo (2598 in CYD14 and 6940 in CYD15) were 6 to 16 years of age.

At the start of the CYD14 and CYD15 studies, dengue seroprevalence for the overall population at the study sites ranged from 52.8%-81.1% in CYD14 (Asia-Pacific) and 55.7%-92.7% in CYD15 (Latin America).

The efficacy was assessed during an Active Phase of 25 months, in which surveillance was designed to maximize the detection of all symptomatic virologically-confirmed dengue (VCD) cases regardless of the severity. The active detection of symptomatic dengue cases started on the day of the first injection and lasted until 13 months after the third injection.

For the primary endpoint, the incidence of symptomatic VCD cases occurring during the 12-month period from 28 days after the third injection was compared between the vaccine and the Control Group.

Exploratory vaccine efficacy analyses according to dengue serostatus measured by plaque reduction neutralization test (PRNT50) at baseline (before the first injection) were performed in the immunogenicity subset of 2000 subjects each in CYD14 and CYD15 and 300 subjects in CYD23. Of the 2580 subjects 6 to 16 years old in this subset (approximately 80%) who were dengue seropositive at baseline, 1729 subjects received the vaccine (656 subjects in CYD14 and 1073 in CYD15) and 851 subjects received placebo (339 in CYD14 and 512 in CYD15) (see also subsection Immunogenicity).

Clinical efficacy data for subjects 6 to 16 years of age in endemic areas, any serostatus at baseline

The Vaccine Efficacy (VE) results according to the primary endpoint (symptomatic VCD cases occurring during the 25-month period after the first dose) in subjects 6 to 16 years of age (any serostatus at baseline) are shown in **Table 2** for studies CYD14, CYD15 and CYD23.

Table 2: VE against symptomatic VCD cases during the 25-month period after the first dose due to any of the 4 serotypes in subjects 6 to 16 years (any serostatus at baseline).

	CYD14		CYD15		CYD23		Pooled CYD14+CYD15		Pooled* CYD14+CYD15+ CYD23	
	Vaccine group	Control group	Vaccine group	Control group	Vaccine group	Control group	Vaccine group	Control group	Vaccine group	Control group
Cases / person-years	166/10352	220/5039	227/26883	385/13204	62/4336	46/2184	393/37235	605/18243	455/41571	651/20427
VE % (95%CI)	63.3 (54.9 ; 70.2)		64.7 (58.7; 69.8)		32.1 (-1.7; 54.4)		64.2 (59.6; 68.4)		62.0 (57.3; 66.2)	

N: number of subjects per study

Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode in the considered period.

Person-years: sum of time-at-risk (in years) for the subjects during the study period.

CI: confidence interval.

*Pooled results of CYD14, 15 and 23 need to be interpreted cautiously because of differences in the Dengue confirmatory test and acute febrile illness definition between CYD14/15 and CYD23.

In subjects 6 to 16 years of age, the efficacy of Dengvaxia against symptomatic virologically-confirmed dengue (VCD) cases due to any of the 4 serotypes was demonstrated in all three studies, CYD14, CYD15 and CYD23 (see **Table 2**).

Clinical efficacy data for subjects 6 to 16 years of age in endemic areas, dengue seropositive at baseline

VE against symptomatic VCD cases in subjects 6 to 16 years of age

The Vaccine Efficacy (VE) results according to exploratory analysis of symptomatic VCD cases occurring during the 25-month period after the first dose in subjects 6 to 16 years of age, seropositives at baseline are shown in **Table 3** for the immunogenicity subset of studies CYD14, CYD15 and CYD23.

Table 3: VE against symptomatic VCD cases during the 25-month period after the first dose due to any of the 4 serotypes in subjects 6 to 16 years (dengue seropositive at baseline).

	CYD14		CYD15		CYD23		Pooled CYD14+CYD15		Pooled * CYD14+CYD15+ CYD23	
	Vaccine group	Control group	Vaccine group	Control group	Vaccine group	Control group	Vaccine group	Control group	Vaccine group	Control group
Cases / person-years	12/1320	25/671	8/2116	23/994	2/248	5/114	20/3436	48/1665	22/3684	53/1779
VE % (95%CI)	75.6 (49.6; 88.8)		83.7 (62.2; 93.7)		81.6 (-12.6; 98.2)		79.7 (65.7; 87.9)		79.9 (66.9; 87.7)	

N: number of subjects per study

Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode in the considered period.

Person-years: sum of time-at-risk (in years) for the subjects during the study period.

CI: confidence interval.

NC: Not computed (the absence of cases in vaccine and control group does not permit to calculate VE nor CI)

*Pooled results of CYD14, 15 and 23 need to be interpreted cautiously because of differences in the Dengue confirmatory test and acute febrile illness definition between CYD14/15 and CYD23.

The four serotypes contributed to the overall Vaccine Efficacy (VE). Data are limited because baseline immunostatus was initially collected in a limited subset of subjects. VE against symptomatic VCD due to serotype 1 [76.8 (46.1; 90.0)] and to serotype 2 [55.5 (-15.5; 82.8)] tends to be lower compared to

serotypes 3 [89.6 (63.7; 97.0)] and serotype 4 [96.5 (73.4; 99.5)] during the 25-month period after the first dose, for subjects 6 to 16 years who are seropositive at baseline (immunogenicity subset of studies CYD14, CYD15 and CYD23).

Efficacy tends to be slightly lower in the 6-8 years of age compared to children 9-16 years of age.

VE against hospitalized and severe VCD cases in subjects 6 to 16 years of age

In subjects 6 to 16 years of age, dengue seropositive at baseline (immunogenicity subset), two clinically severe VCD cases in CYD14 and one in CYD15 were reported during the 25-month period after the first injection in the control group versus none in the vaccine group. Eight hospitalized VCD cases in CYD14 were reported in the control group versus one in the vaccine group and two hospitalized VCD cases in CYD15 were reported in the control group versus none in the vaccine group. These data are inconclusive due to the low number of cases in the immunogenicity subset.

Efficacy was assessed in moderate-high endemic areas. The magnitude of protection may not be extrapolated to other epidemiological situations.

Clinical efficacy data for subjects 17 to 45 years of age in endemic areas

No clinical efficacy study has been done in subjects from 17 to 45 years from endemic areas. The clinical efficacy of the vaccine is based on bridging of immunogenicity data (see below section *Immunogenicity data for subjects 18 to 45 years of age in endemic areas*).

Long-term protection

Limited data suggest a trend for efficacy to decrease over time. During the last 2 years of follow-up (Year 5 and 6) after the initial dose, vaccine efficacy against symptomatic VCD (Immunogenicity Subset, pooled CYD14+CYD15) was 14.6% (95% CI: -74.7; 58.3) in subjects 6 to 16 years with previous dengue infection. Efficacy persistence may vary according to the epidemiological situations.

Immunogenicity

No immune correlate of protection has been established. During clinical development, immunogenicity data were collected in a total of 7262 subjects 9 months to 60 years of age that received at least one injection of the vaccine.

Among these subjects, a total of 3498 subjects 6 to 45 years of age from endemic areas and dengue immune received at least one injection of Dengvaxia. Most of the subjects were 6 to 17 years of age (n=2836).

During clinical development, neutralizing antibody titres for each serotype were measured with the plaque reduction neutralization test (PRNT) and presented as geometric mean titres (GMTs).

In the following Tables the dengue serostatus at baseline (before the first injection), was defined as:

- Dengue seropositivity if the PRNT50 titre ≥ 10 [1/dil] (the lower limit of quantification, LLOQ), against at least one serotype.
- Dengue seronegativity if the PRNT50 titre < the lower limit of quantification against any of the 4 serotypes.

Immunogenicity data for subjects 6 to 8 years of age in endemic areas

GMTs at baseline and 28 days post-dose 3 in subjects 6 to 8 years of age in CYD14 are shown in the Table 4.

Table 4: Immunogenicity for dengue seropositive subjects 6 to 8 years of age in CYD14 from endemic areas

		Serotype 1		Serotype 2		Serotype 3		Serotype 4	
Study	N	Pre-dose 1 GMT (95%CI)	Post-dose 3 GMT (95%CI)	Pre-dose 1 GMT (95%CI)	Post-dose 3 GMT (95%CI)	Pre-dose 1 GMT (95%CI)	Post-dose 3 GMT (95%CI)	Pre-dose 1 GMT (95%CI)	Post-dose 3 GMT (95%CI)
CYD14	168	80.8 (57.3; 114)	203 (154; 268)	118 (86.0; 161)	369 (298; 457)	105 (75.5; 145)	316 (244; 411)	48.4 (37.2; 63.0)	175 (145; 211)

N: number of subjects with available antibody titre for the relevant endpoint

Dengue seropositive subjects are subjects with titres above or equal to LLOQ against at least one dengue serotype at baseline

CI: Confidence Interval

CYD14: Indonesia, Malaysia, the Philippines, Thailand, Vietnam.

Immunogenicity data for subjects 9 to 17 years of age in endemic areas

GMTs at baseline and 28 days post-dose 3 in subjects 9 to 16 years of age in CYD14 and CYD15 are shown in the Table 5.

Table 5: Immunogenicity for dengue seropositive subjects 9 to 16 years of age in CYD14 and CYD15 from endemic areas

		Serotype 1		Serotype 2		Serotype 3		Serotype 4	
Study	N	Pre-injection 1 GMT (95%CI)	Post-injection 3 GMT (95%CI)	Pre-injection 1 GMT (95%CI)	Post-injection 3 GMT (95%CI)	Pre-injection 1 GMT (95%CI)	Post-injection 3 GMT (95%CI)	Pre-injection 1 GMT (95%CI)	Post-injection 3 GMT (95%CI)
CYD14	485	167 (138; 202)	437(373; 511)	319 (274; 373)	793(704; 892)	160 (135; 190)	443(387; 507)	83.8 (72.0; 97.6)	272(245; 302)
CYD15	1048	278 (247; 313)	703(634; 781)	306 (277; 338)	860(796; 930)	261 (235; 289)	762(699; 830)	73.3 (66.6; 80.7)	306(286; 328)

N: number of subjects with available antibody titre for the relevant endpoint

Dengue seropositive subjects are subjects with titres above or equal to LLOQ against at least one dengue serotype at baseline

CI: Confidence Interval

CYD14: Indonesia, Malaysia, the Philippines, Thailand, Vietnam.

CYD15: Brazil, Colombia, Honduras, Mexico, Puerto Rico.

Immunogenicity data for subjects 18 to 45 years of age in endemic areas

The immunogenicity of the final formulation of the CYD dengue vaccine in adults aged 18 to 45 years in endemic areas was assessed in 3 studies conducted all in Asia-Pacific (CYD22 in Vietnam, CYD28 in Singapore and CYD47 in India).

GMTs at baseline and 28 days post-dose 3 in subjects 18 to 45 years of age are shown in the Table 6

Table 6: Immunogenicity for dengue seropositive subjects 18 to 45 years of age from endemic areas

		Serotype 1		Serotype 2		Serotype 3		Serotype 4	
Study	N	Pre-injection 1 GMT (95%CI)	Post-injection 3 GMT (95%CI)	Pre-injection 1 GMT (95%CI)	Post-injection 3 GMT (95%CI)	Pre-injection 1 GMT (95%CI)	Post-injection 3 GMT (95%CI)	Pre-injection 1 GMT (95%CI)	Post-injection 3 GMT (95%CI)
CYD22	19	408 (205; 810)	785 (379; 1626)	437 (240; 797)	937 (586; 1499)	192 (117; 313)	482 (357; 651)	86.5 (41.2; 182)	387 (253; 591)
CYD28	66	59.8 (36.8;97.4)	235 (135; 409)	67.1 (40.9; 110)	236 (144; 387)	48.4 (32.9;71.0)	239 (166; 342)	22.1 (14.7;33.4)	211 (155; 287)
CYD47	109	324 (236; 445)	688 (524; 901)	363 (269; 490)	644 (509; 814)	394 (299; 519)	961 (763; 1211)	80.7 (613; 106)	413(331; 516)

N: number of subjects with available antibody titre for the relevant endpoint

Dengue seropositive subjects are subjects with titres above or equal to LLOQ against at least one dengue serotype at baseline

CI: Confidence Interval

CYD28: Low endemic country

CYD22: Vietnam; CYD28: Singapore; CYD47: India;

The bridging of efficacy is based on above available data and overall results. Immunogenicity data available from studies in adults aged 18 to 45 years in endemic regions show that post-injection 3 GMTs against each serotype are generally higher in adults than in children and adolescents in CYD14 and CYD15. Therefore, protection is expected in adults in endemic areas although the actual magnitude of efficacy relative to that observed in children and adolescents is unknown.

Long-term persistence of antibodies

The GMTs persisted post dose 3 up to 5 years in subjects 6 years of age and older in studies CYD14 and CYD15. At year 5 after the third injection, GMTs were still higher to pre-vaccination GMTs despite decrease in the GMTs against all 4 serotypes compared to post-dose 3 GMTs. The GMTs levels depend on age and dengue serostatus at baseline.

The effect of a booster dose was assessed in subjects 9-50 years living in endemic areas after a 3-dose schedule (studies CYD63, CYD64, CYD65). No or modest transient increase of neutralizing Ab titers was observed after the boost. The booster effect was variable across serotypes and studies. Why there is a lack/limited booster effect with Dengvaxia remains not understood in terms of mechanisms and clinical implications.

5.2 Pharmacokinetic properties

No pharmacokinetic studies have been performed on Dengvaxia.

5.3 Preclinical safety data

Non-clinical safety data revealed no special risks for humans based on a repeated-dose toxicity including assessment of local tolerance, and a developmental and reproductive toxicology program. A neurovirulence study shows that CYD dengue vaccine is not neurotoxic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Essential amino acids including Phenylalanine

Non-essential amino acids

Arginine hydrochloride

Sucrose

Trehalose dihydrate

Sorbitol (E420)

Trometamol

Urea

Hydrochloric acid and sodium hydroxide for pH adjustment

Solvent:

Sodium chloride

Water for injections

6.2 Incompatibilities

Dengvaxia must not be mixed with any other vaccine or medicinal product.

6.3 Shelf life

3 years

After reconstitution with the solvent provided, Dengvaxia must be kept in a refrigerator (2°C to 8°C) and must be used within 6 hours.

6.4 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 6.3.

6.5 Nature and contents of container

- Powder (5 doses) in vial (Type-I glass), with a stopper (halobutyl) and a flip-off cap (aluminium, polypropylene) + 2.5 mL of solvent in vial (Type-I glass), with a stopper (halobutyl) and a flip-off cap (aluminium, polypropylene).

Pack size of 5.

6.6 Special precautions for disposal and other handling

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

Dengvaxia must be reconstituted prior to administration.

Dengvaxia is reconstituted by transferring all of the solvent (0.9% sodium chloride solution) provided in the 5-dose vial with a dark gray flip-off cap into the 5-dose vial of freeze-dried powder with a medium brown flip-off cap, using a sterile syringe and needle.

1. Use a sterile syringe and needle for the transfer of the solvent.
2. Transfer the entire content of the solvent vial (with a dark gray flip-off cap) into the vial containing the powder (medium brown flip-off cap).
3. Swirl gently until the powder is completely dissolved.

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

After complete dissolution, a 0.5 mL dose of the reconstituted suspension is withdrawn into the same syringe. A new sterile syringe and needle should be used for withdrawal of each of the 5 doses. The recommended size of the needle to be used is 23G or 25G.

Before each injection, the reconstituted suspension should be gently swirled once again.

After reconstitution with the solvent provided, Dengvaxia must be used within 6 hours.

Partially used vials must be kept between 2°C and 8°C (in a refrigerator) and protected from light.

Any remaining vaccine doses should be discarded at the end of the immunization session or within 6 hours after reconstitution, whichever comes first.

A partially used multidose vial must be discarded immediately if:

- Sterile dose withdrawal has not been fully observed.
- A new sterile syringe and needle were not used for reconstitution or withdrawal of each of the previous doses.
- There is any suspicion that the partially used vial has been contaminated.
- There is visible evidence of contamination, such as a change in appearance.

Any unused product or waste material should be disposed of in accordance with local regulations.

7. MARKETING AUTHORISATION HOLDER

Sanofi Pasteur
14 Espace Henry Vallée
69007 Lyon
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1338/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 December 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE
SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE
FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY
AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO
THE SAFE AND EFFECTIVE USE OF THE MEDICINAL
PRODUCT**

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Sanofi Pasteur NVL
31-33 quai Armand Barbès
69250 Neuville-sur-Saône
France

Sanofi Pasteur
1541 avenue Marcel Mérieux
69280 Marcy l'Etoile
France

Name and address of the manufacturer(s) responsible for batch release

Sanofi Pasteur NVL
31-33 quai Armand Barbès
69250 Neuville-sur-Saône
France

Sanofi Pasteur
Parc Industriel d'Incarville
27100 Val de Reuil
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing

authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Dengvaxia in each Member State the Marketing Authorisation Holder (MAH) must agree the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Dengvaxia is marketed, all healthcare professionals who are expected to use Dengvaxia have access to/are provided with the following educational package:

- Physician educational material

The physician educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals

The Guide for healthcare professionals shall contain the following key elements:

- That there is an increased risk of severe and/or hospitalized dengue following vaccination in individuals not previously infected by dengue virus;
- That healthcare professionals have to document before vaccination the previous dengue infection, which has to be assessed by laboratory confirmed history of dengue or through serotesting;
- The healthcare professionals should be aware that the test they use should have adequate performance in terms of specificity and cross-reactivity based on the local disease epidemiology.
- That healthcare professionals should be aware of dengue early warning signs.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Powder (1 dose) in vial + 0.5 mL of solvent in pre-filled syringe with 2 separate needles.
Powder (1 dose) in vial + 0.5 mL of solvent in pre-filled syringe.
Pack size of 1 or 10.

1. NAME OF THE MEDICINAL PRODUCT

Dengvaxia, powder and solvent for suspension for injection in pre-filled syringe
dengue tetravalent vaccine (live, attenuated)

2. STATEMENT OF ACTIVE SUBSTANCES

After reconstitution, one dose (0.5 mL) contains 4.5 - 6.0 log₁₀ CCID₅₀ of each serotype of the chimeric yellow fever dengue virus (1, 2, 3 and 4) (live, attenuated).

3. LIST OF EXCIPIENTS

Excipients:

Powder: essential amino acids including Phenylalanine, non-essential amino acids, Arginine hydrochloride, sucrose, Trehalose dihydrate, Sorbitol, trometamol, urea, hydrochloric acid, sodium hydroxide.

Solvent: sodium chloride (0.4%), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder (1 dose) in vial + 0.5 mL of solvent in pre-filled syringe with 2 separate needles
Powder (1 dose) in vial + 0.5 mL of solvent in pre-filled syringe
Pack size of 1 or 10

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use after reconstitution.
Read the package leaflet before use and for reconstitution instructions.
Reconstitute Dengvaxia with the solvent provided.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze. Protect from light.
After reconstitution, use immediately.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Sanofi Pasteur
14 Espace Henry Vallée
69007 Lyon
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1338/001
EU/1/18/1338/002
EU/1/18/1338/003
EU/1/18/1338/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**Dengvaxia - Powder (1 dose) in vial****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Dengvaxia, powder for injection
dengue tetravalent vaccine (live, attenuated)
SC

2. METHOD OF ADMINISTRATION**3. EXPIRY DATE**

EXP {MM/YYYY}

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 Dose
1D

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**Dengvaxia - Solvent in a pre-filled syringe (0.5 mL)****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Solvent for reconstitution of Dengvaxia
NaCl (0.4%)

2. METHOD OF ADMINISTRATION**3. EXPIRY DATE**

EXP {MM/YYYY}

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 Dose - 0.5 mL
1D

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**Dengvaxia - Powder (5 doses) in vial + 2.5 mL of solvent in vial. Pack size of 5****1. NAME OF THE MEDICINAL PRODUCT**

Dengvaxia, powder and solvent for suspension for injection in multidose containers
dengue tetravalent vaccine (live, attenuated)

2. STATEMENT OF ACTIVE SUBSTANCES

After reconstitution, one dose (0.5 mL) contains 4.5 - 6.0 log₁₀ CCID₅₀ of each serotype of the chimeric yellow fever dengue virus (1, 2, 3 and 4) (live, attenuated).

3. LIST OF EXCIPIENTS

Excipients:

Powder: essential amino acids including Phenylalanine, non-essential amino acids, Arginine hydrochloride, sucrose, Trehalose dihydrate, Sorbitol, trometamol, urea, hydrochloric acid, sodium hydroxide.

Solvent: sodium chloride (0.9%), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder (5 doses) in vial + 2.5 mL of solvent in vial
Pack size of 5.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use after reconstitution.
Read the package leaflet before use and for reconstitution instructions.
Reconstitute Dengvaxia with the solvent provided.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze. Protect from light.

After reconstitution, use within 6 hours if stored between 2°C and 8°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Sanofi Pasteur
14 Espace Henry Vallée
69007 Lyon
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1338/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Dengvaxia - Powder (5 doses) in vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

Dengvaxia, powder for injection
dengue tetravalent vaccine (live, attenuated)
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

5 Doses
5D

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**Dengvaxia - Solvent in vial (2.5 mL)****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Solvent for reconstitution of Dengvaxia
NaCl (0.9%)

2. METHOD OF ADMINISTRATION**3. EXPIRY DATE**

EXP {MM/YYYY}

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 Doses - 2.5 mL
5D

6. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the User

Dengvaxia, powder and solvent for suspension for injection in pre-filled syringe dengue tetravalent vaccine (live, attenuated)

Read all of this leaflet carefully before you or your child is vaccinated because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This vaccine has been prescribed for you or your child only. Do not pass it on to others.
- If you or your child get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Dengvaxia is and what it is used for
2. What you need to know before you or your child use Dengvaxia
3. How to use Dengvaxia
4. Possible side effects
5. How to store Dengvaxia
6. Contents of the pack and other information

1. What Dengvaxia is and what it is used for

Dengvaxia is a vaccine. It is used to help protect you or your child against "dengue disease" caused by dengue virus serotypes 1, 2, 3 and 4. It contains versions of these 4 varieties of the virus that have been weakened so that they cannot cause the disease.

Dengvaxia is given to adults, young people and children (from 6 to 45 years of age) with prior dengue virus infection confirmed by a test (also see sections 2 and 3).

Dengvaxia should be used according to official recommendations.

How the vaccine works

Dengvaxia stimulates the body's natural defences (immune system), to produce antibodies that will help protect against the viruses that cause dengue disease if the body is exposed to them in the future.

What is dengue and dengue disease?

Dengue is a viral infection which spreads through the bite of an infected *Aedes* mosquito. The virus from an infected person can spread to other people through mosquito bites for about 4 to 5 days (maximum 12 days) after the first symptoms appear. Dengue is not transmitted directly from person-to-person.

Dengue disease results in symptoms including fever, headache, pain behind the eyes, muscle and joint pain, feeling sick (nausea), being sick (vomiting), swollen glands or skin rash. Symptoms usually last for 2 to 7 days. You can also have dengue but show no symptoms (called "asymptomatic").

Occasionally dengue can be severe enough for you to have to go to the hospital and in rare cases it can cause death. Severe dengue can give you a high fever and any of the following: severe abdominal (belly) pain, persistent sickness (vomiting), rapid breathing, severe bleeding, bleeding in the stomach, bleeding gums, feeling tired, feeling restless, coma, having fits (seizures) and organ failure.

2. What you need to know before you or your child use Dengvaxia

To make sure that Dengvaxia is suitable for you or your child, it is important to tell your doctor, pharmacist or nurse if any of the points below apply to you or your child. If there is anything you do not understand, ask your doctor, pharmacist or nurse to explain.

Do not use Dengvaxia if you or your child

- Know you are allergic to the active substances or any of the other ingredients of Dengvaxia (listed in section 6).
- had an allergic reaction after using Dengvaxia before. Signs of an allergic reaction may include an itchy rash, shortness of breath and swelling of the face and tongue.
- have a weak immune system (the body's natural defences). This may be due to a genetic defect or HIV infection.
- are taking a medicine that affects the immune system (such as high-dose corticosteroids or chemotherapy). Your doctor will not use Dengvaxia until 4 weeks after you stop treatment.
- are pregnant or breast-feeding.

Warnings and precautions

Being vaccinated without having been priorly infected by dengue virus may lead to an increased risk of a more serious dengue illness. This could lead to hospitalisation if you are later bitten by a dengue-infected mosquito.

Before the administration of Dengvaxia, your doctor, pharmacist or nurse will check if you or your child have ever been infected by dengue virus, and will tell you if a test has to be performed.

Tell your doctor, pharmacist or nurse before using Dengvaxia if you or your child have:

- a mild to high fever or acute disease. You will not get Dengvaxia until you or your child have recovered.
- ever had any health problems when given a vaccine. Your doctor will carefully consider the risks and benefits of vaccination.
- ever fainted from an injection. Fainting, and sometime falling, can occur (mostly in young people) following, or even before, any injection with a needle.
- had any allergic reaction to latex. The tip cap of the pre-filled syringe contains a natural rubber latex which may cause an allergic reaction.

Travellers

Vaccination is not recommended if you have never lived in an area where dengue infections regularly occur and if you plan to only occasionally travel to an area where dengue infections regularly occur.

Important information about the protection provided

As with any vaccines, Dengvaxia may not protect everybody who has been vaccinated. You must continue to protect yourself against mosquito bites even after vaccination.

After vaccination, you should consult a doctor if you or your child believe you might have a dengue infection, and develop any of the following symptoms: high fever, severe abdominal pain, persistent vomiting, rapid breathing, bleeding gums, tiredness, restlessness and blood in vomit.

Additional protection precautions

You should take precautions to prevent mosquito bites. This includes using insect repellents, wearing protective clothing, and using mosquito nets.

Younger children

Do not give this vaccine to children less than 6 years of age because safety and efficacy of Dengvaxia have not been established.

Other medicines or vaccines and Dengvaxia

Tell your doctor or pharmacist if you or your child are using, have recently used or might use any other vaccines or medicines.

In particular, tell your doctor or pharmacist if you are taking any of the following:

- medicines that affect your body's natural defences (immune system) such as high-dose corticosteroids or chemotherapy. In this case, your doctor will not use Dengvaxia until 4 weeks after you stop treatment. This is because Dengvaxia might not work as well.
- medicines called "immunoglobulins" or blood products containing immuno globulins, such as blood or plasma. In this case, your doctor will not use Dengvaxia until 6 weeks, and preferably not for 3 months after you stop treatment. This is because Dengvaxia might not work as well.

Dengvaxia can be given at the same time as Diphtheria, Tetanus, Pertussis vaccine or recombinant Human Papillomavirus vaccines. Injections of more than one vaccine at the same time should be given at different injection sites.

Pregnancy and breast-feeding

Do not use Dengvaxia if you or your daughter are pregnant or breast-feeding. If you or your daughter:

- are of child-bearing age, you must use an effective method of contraception to avoid pregnancy for at least one month after each Dengvaxia dose.
- think you or your daughter may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before using Dengvaxia.

Driving and using machines

Dengvaxia has minor influence on the ability to drive and use machines.

Dengvaxia contains phenylalanine, sodium and sorbitol

Dengvaxia contains 41 micrograms of phenylalanine in each 0.5 ml dose. Phenylalanine may be harmful if you have 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.

3. How to use Dengvaxia

Previous dengue infection must be confirmed by a test, either documented in the medical history or performed prior to vaccination.

Dengvaxia is given by your doctor or nurse as an injection under the skin (subcutaneous injection) in the upper arm. It must not be injected into a blood vessel.

You or your child will receive 3 injections of 0.5 mL – one every 6 months.

- The first injection will be given at the chosen or scheduled date.
- The second injection, 6 months after the first injection.
- The third injection, 6 months after the second injection.

Dengvaxia should be used according to official recommendations.

Instructions for preparing the vaccine intended for medical and healthcare professionals are included at the end of the leaflet.

If you or your child miss an injection of Dengvaxia

- If you or your child miss a scheduled injection, your doctor will decide when to give the missed injection. It is important that you or your child follow the instructions of your doctor, pharmacist or nurse regarding follow-up injection.
- If you forget or are not able to go back at the schedule time, ask your doctor, pharmacist or nurse for advice.

If you have any further questions on the use of this product, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, Dengvaxia can cause side effects, although not everybody gets them.

Serious allergic (anaphylactic) reactions

If any of these symptoms occur after leaving the place where you or your child received an injection, **contact a doctor immediately:**

- difficulty breathing
- blueness of the tongue or lips
- a rash
- swelling of the face or throat
- low blood pressure causing dizziness or fainting
- sudden and serious feeling of illness or unease with drop in blood pressure causing dizziness and loss of consciousness, rapid heartbeat linked with breathing difficulty.

These signs or symptoms (anaphylactic reactions) usually develop soon after the injection is given and while you or your child are still in the clinic or doctor's surgery. They can also happen very rarely after receiving any vaccine (may affect up to 1 in 10 000 people).

Other serious reactions

For some people who have not been infected by dengue before vaccination, there may be an increased risk of getting a more serious dengue illness requiring hospitalisation if they become bitten by a dengue-infected mosquito later. This increased risk may mainly begin during the third year following the first injection.

Other side effects

The following side effects occurred during studies in children, young people and adults. Most of the side effects occurred within 3 days of having the injection of Dengvaxia.

Very common: (may affect more than 1 in 10 people)

- headache
- muscle pain (myalgia)
- generally feeling unwell (malaise)
- weakness (asthenia)
- injection site reactions: pain and redness (erythema)
- fever.

Common: (may affect up to 1 in 10 people)

- injection site reactions: bruising (haematoma), swelling, and itching (pruritus).

Uncommon: (may affect up to 1 in 100 people)

- infections of the nose or throat (upper respiratory tract)
- pain or swelling of the nose or throat (nasopharyngitis)
- feeling dizzy
- sore throat (oropharyngeal pain)
- cough
- feeling sick (nausea)

- vomiting
- rash (skin eruption)
- neck pain
- chills
- hardening of skin at the injection site (injection site induration)
- injection site haemorrhage.

Very rare: (may affect up to 1 in 10 000 people)

- allergic reactions.

Additional side effects in adults:

Uncommon: (may affect up to 1 in 100 people)

- swollen glands (lymphadenopathy)
- dry mouth
- joint pain (arthralgia)
- injection site warmth
- fatigue.

Additional side effects in children and adolescents (from 6 to and including 17 years of age):

Rare: (may affect up to 1 in 1000 people)

- runny nose (rhinorrhea)
- itchy rash (urticaria).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Dengvaxia

Keep Dengvaxia out of the sight and reach of children.

Do not use Dengvaxia after the expiry date that is stated on the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Keep the vaccine in the outer carton in order to protect it from light.

After mixing (reconstitution) with the solvent provided, the product should be used immediately.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Dengvaxia contains

- After reconstitution, one dose (0.5 mL) contains 4.5 - 6.0 log₁₀ CCID₅₀* of each serotype of the chimeric yellow fever dengue virus** (1, 2, 3 and 4) (live, attenuated).
* CCID₅₀: 50% Cell Culture Infectious Dose.
** Produced in Vero cells by recombinant DNA technology. This product contains genetically

modified organisms (GMOs).

- The other ingredients are: essential amino acids including Phenylalanine, non-essential amino acids, Arginine hydrochloride, Sucrose, Trehalose dihydrate, Sorbitol (E420), trometamol, urea, sodium chloride, water for injections and hydrochloric acid and sodium hydroxide for pH adjustment.

What Dengvaxia looks like and contents of the pack

Dengvaxia is a powder and solvent for suspension for injection. Dengvaxia is provided as a powder in a single-dose vial and a solvent in single-dose pre-filled syringe (0.5 mL) with 2 separate needles or with no needle. The powder and the solvent must be mixed together before use.

Dengvaxia is available in packs of 1 or 10. Not all pack sizes may be marketed.

The powder is a white, homogenous, freeze-dried powder with possible retraction at the base (ring-shaped cake possible).

The solvent (0.4% sodium chloride solution) is a clear and colourless solution.

After reconstitution with the solvent provided, Dengvaxia is a clear, colourless liquid with the possible presence of white to translucent particles.

Marketing Authorisation Holder:

Sanofi Pasteur
14 Espace Henry Vallée
69007 Lyon
France

Manufacturer:

SANOFI PASTEUR
Parc Industriel d'Incarville
27100 Val de Reuil
France

Or

SANOFI PASTEUR NVL
31-33 Quai Armand Barbès
69250 Neuville-sur-Saône
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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España sanofi-aventis, S.A. Tel: +34 93 485 94 00	Polska Sanofi Pasteur Sp. z o.o. Tel.: +48 22 280 00 00
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Ireland sanofi-aventis Ireland T/A SANOFI Tel: + 353 (0) 1 4035 600	Slovenija Swixx Biopharma d.o.o. Tel.: +386 1 235 51 00
Ísland Vistor Tel : +354 535 7000	Slovenská republika Swixx Biopharma s.r.o. Tel.: +421 2 208 33 600
Italia Sanofi S.r.l. Tel: 800536389 Tel dall'estero: +39 02 39394983	Suomi/Finland Sanofi Oy Tel: +358 (0) 201 200 300
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This leaflet was last revised in [{MM/YYYY}].

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

- As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in the event of an anaphylactic reaction following the administration of Dengvaxia.
- Dengvaxia must not be mixed with other medicinal products in the same syringe.
- Dengvaxia must not be administered by intravascular injection under any circumstances.
- Immunisation should be carried out by subcutaneous (SC) injection preferably in the upper arm in the region of the deltoid.
- 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.

Reconstitution and handling of single-dose pack size

Dengvaxia must be reconstituted prior to administration.

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.

1. Attach a sterile needle to the pre-filled syringe for the transfer of the solvent. The needle must be fitted firmly to the syringe, rotating it by a one-quarter turn.
2. Transfer the entire content of the pre-filled syringe into the vial containing the powder.
3. Swirl gently until the powder is completely dissolved.

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

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.

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

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

Any unused product or waste material should be disposed of in accordance with local regulations.

Package Leaflet: Information for the User

Dengvaxia, powder and solvent for suspension for injection in multidose containers dengue tetravalent vaccine (live, attenuated)

Read all of this leaflet carefully before you or your child is vaccinated because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This vaccine has been prescribed for you or your child only. Do not pass it on to others.
- If you or your child get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Dengvaxia is and what it is used for
2. What you need to know before you or your child use Dengvaxia
3. How to use Dengvaxia
4. Possible side effects
5. How to store Dengvaxia
6. Contents of the pack and other information

1. What Dengvaxia is and what it is used for

Dengvaxia is a vaccine. It is used to help protect you or your child against "dengue disease" caused by dengue virus serotypes 1, 2, 3 and 4. It contains versions of these 4 varieties of the virus that have been weakened so that they cannot cause the disease.

Dengvaxia is given to adults, young people and children (from 6 to 45 years of age) with prior dengue virus infection confirmed by a test (also see sections 2 and 3).

Dengvaxia should be used according to official recommendations.

How the vaccine works

Dengvaxia stimulates the body's natural defences (immune system), to produce antibodies that will help protect against the viruses that cause dengue disease if the body is exposed to them in the future.

What is dengue and dengue disease?

Dengue is a viral infection which spreads through the bite of an infected *Aedes* mosquito. The virus from an infected person can spread to other people through mosquito bites for about 4 to 5 days (maximum 12 days) after the first symptoms appear. Dengue is not transmitted directly from person-to-person.

Dengue disease results in symptoms including fever, headache, pain behind the eyes, muscle and joint pain, feeling sick (nausea), being sick (vomiting), swollen glands or skin rash. Symptoms usually last for 2 to 7 days. You can also have dengue but show no symptoms (called "asymptomatic").

Occasionally dengue can be severe enough for you to have to go to hospital and in rare cases it can cause death. Severe dengue can give you a high fever and any of the following: severe abdominal (belly) pain, persistent sickness (vomiting), rapid breathing, severe bleeding, bleeding in the stomach, bleeding gums, feeling tired, feeling restless, coma, having fits (seizures) and organ failure.

2. What you need to know before you or your child use Dengvaxia

To make sure that Dengvaxia is suitable for you or your child, it is important to tell your doctor, pharmacist or nurse if any of the points below apply to you or your child. If there is anything you do not understand, ask your doctor, pharmacist or nurse to explain.

Do not use Dengvaxia if you or your child

- Know you are allergic to the active substances or any of the other ingredients of Dengvaxia (listed in section 6).
- had an allergic reaction after using Dengvaxia before. Signs of an allergic reaction may include an itchy rash, shortness of breath and swelling of the face and tongue.
- have a weak immune system (the body's natural defences). This may be due to a genetic defect or HIV infection.
- are taking a medicine that affects the immune system (such as high-dose corticosteroids or chemotherapy). Your doctor will not use Dengvaxia until 4 weeks after you stop treatment.
- are pregnant or breast-feeding.

Warnings and precautions

Being vaccinated without having been priorly infected by dengue virus may lead to an increased risk of a more serious dengue illness. This could lead to hospitalisation if you are later bitten by a dengue-infected mosquito.

Before the administration of Dengvaxia, your doctor, pharmacist or nurse will check if you or your child have ever been infected by dengue virus, and will tell you if a test has to be performed.

Tell your doctor, pharmacist or nurse before using Dengvaxia if you or your child have:

- a mild to high fever or acute disease. You will not get Dengvaxia until you or your child have recovered.
- ever had any health problems when given a vaccine. Your doctor will carefully consider the risks and benefits of vaccination.
- ever fainted from an injection. Fainting, and sometime falling, can occur (mostly in young people) following, or even before, any injection with a needle.

Travellers

Vaccination is not recommended if you have never lived in an area where dengue infections regularly occur and if you plan to only occasionally travel to an area where dengue infections regularly occur.

Important information about the protection provided

As with any vaccines, Dengvaxia may not protect everybody who has been vaccinated. You must continue to protect yourself against mosquito bites even after vaccination.

After vaccination, you should consult a doctor if you or your child believe you might have a dengue infection, and develop any of the following symptoms: high fever, severe abdominal pain, persistent vomiting, rapid breathing, bleeding gums, tiredness, restlessness and blood in vomit.

Additional protection precautions

You should take precautions to prevent mosquito bites. This includes using insect repellents, wearing protective clothing, and using mosquito nets.

Younger children

Do not give this vaccine to children less than 6 years of age because safety and efficacy of Dengvaxia have not been established.

Other medicines and Dengvaxia

Tell your doctor or pharmacist if you or your child are using, have recently used or might use any other vaccines or medicines.

In particular, tell your doctor or pharmacist if you are taking any of the following:

- medicines that affect your body's natural defences (immune system) such as high-dose corticosteroids or chemotherapy. In this case, your doctor will not use Dengvaxia until 4 weeks after you stop treatment. This is because Dengvaxia might not work as well.
- medicines called "immunoglobulins" or blood products containing immuno globulins, such as blood or plasma. In this case, your doctor will not use Dengvaxia until 6 weeks, and preferably not for 3 months after you stop treatment. This is because Dengvaxia might not work as well.

Dengvaxia can be given at the same time as Diphtheria, Tetanus, Pertussis vaccine or recombinant Human Papillomavirus vaccines. Injections of more than one vaccine at the same time should be given at different injection sites.

Pregnancy and breast-feeding

Do not use Dengvaxia if you or your daughter are pregnant or breast-feeding. If you or your daughter:

- are of child-bearing age, you must use an effective method of contraception to avoid pregnancy for at least one month after each Dengvaxia dose.
- think you or your daughter may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before using Dengvaxia.

Driving and using machines

Dengvaxia has minor influence on the ability to drive and use machines.

Dengvaxia contains phenylalanine, sodium and sorbitol

Dengvaxia contains 8 micrograms of phenylalanine in each 0.5 ml dose. Phenylalanine may be harmful if you have 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 1.76 milligrams of sorbitol in each 0.5 ml dose.

3. How to use Dengvaxia

Previous dengue infection must be confirmed by a test, either documented in the medical history or performed prior to vaccination.

Dengvaxia is given by your doctor or nurse as an injection under the skin (subcutaneous injection) in the upper arm. It must not be injected into a blood vessel.

You or your child will receive 3 injections of 0.5 mL – one every 6 months.

- The first injection will be given at the chosen or scheduled date.
- The second injection, 6 months after the first injection.
- The third injection, 6 months after the second injection.

Dengvaxia should be used according to official recommendations.

Instructions for preparing the vaccine intended for medical and healthcare professionals are included at the end of the leaflet.

If you or your child miss an injection of Dengvaxia

- If you or your child miss a scheduled injection, your doctor will decide when to give the missed injection. It is important that you or your child follow the instructions of your doctor, pharmacist or nurse regarding follow-up injection.
- If you forget or are not able to go back at the schedule time, ask your doctor, pharmacist or nurse for advice.

If you have any further questions on the use of this product, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, Dengvaxia can cause side effects, although not everybody gets them.

Serious allergic (anaphylactic) reactions

If any of these symptoms occur after leaving the place where you or your child received an injection, **contact a doctor immediately:**

- difficulty breathing
- blueness of the tongue or lips
- a rash
- swelling of the face or throat
- low blood pressure causing dizziness or fainting
- sudden and serious feeling of illness or unease with drop in blood pressure causing dizziness and loss of consciousness, rapid heartbeat linked with breathing difficulty.

These signs or symptoms (anaphylactic reactions) usually develop soon after the injection is given and while you or your child are still in the clinic or doctor's surgery. They can also happen very rarely after receiving any vaccine (may affect up to 1 in 10 000 people).

Other serious reactions

For some people who have not been infected by dengue before vaccination, there may be an increased risk of getting a more serious dengue illness requiring hospitalisation if they become bitten by a dengue-infected mosquito later. This increased risk may mainly begin during the third year following the first injection.

Other side effects

The following side effects occurred during studies in children, young people and adults. Most of the side effects occurred within 3 days of having the injection of Dengvaxia.

Very common: (may affect more than 1 in 10 people)

- headache
- muscle pain (myalgia)
- generally feeling unwell (malaise)
- weakness (asthenia)
- injection site reactions: pain and redness (erythema)
- fever.

Common: (may affect up to 1 in 10 people)

- injection site reactions: bruising (haematoma), swelling, and itching (pruritus).

Uncommon: (may affect up to 1 in 100 people)

- infections of the nose or throat (upper respiratory tract)
- pain or swelling of the nose or throat (nasopharyngitis)
- feeling dizzy
- sore throat (oropharyngeal pain)
- cough
- feeling sick (nausea)
- vomiting
- rash (skin eruption)
- neck pain
- chills
- hardening of skin at the injection site (injection site induration)
- injection site haemorrhage.

Very rare: (may affect up to 1 in 10 000 people)

- allergic reactions.

Additional side effects in adults:

Uncommon: (may affect up to 1 in 100 people)

- swollen glands (lymphadenopathy)
- dry mouth
- joint pain (arthralgia)
- injection site warmth
- fatigue.

Additional side effects in children and adolescents (from 6 to and including 17 years of age):

Rare: (may affect up to 1 in 1000 people)

- runny nose (rhinorrhea)
- itchy rash (urticaria).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Dengvaxia

Keep Dengvaxia out of the sight and reach of children.

Do not use Dengvaxia after the expiry date that is stated on the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Keep the vaccine in the outer carton in order to protect it from light.

After mixing (reconstitution) with the solvent provided, the product must be used within 6 hours if stored between 2°C and 8°C (i.e., in a refrigerator) and protected from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Dengvaxia contains

- After reconstitution, one dose (0.5 mL) contains 4.5 - 6.0 log₁₀ CCID₅₀* of each serotype of the chimeric yellow fever dengue virus** (1, 2, 3 and 4) (live, attenuated).
* CCID₅₀: 50% Cell Culture Infectious Dose.
** Produced in Vero cells by recombinant DNA technology. This product contains genetically modified organisms (GMOs).
- The other ingredients are: essential amino acids including Phenylalanine, non-essential amino acids, Arginine hydrochloride, Sucrose, Trehalose dihydrate, Sorbitol (E420), trometamol, urea,

sodium chloride, water for injections and hydrochloric acid and sodium hydroxide for pH adjustment.

What Dengvaxia looks like and contents of the pack

Dengvaxia is a powder and solvent for suspension for injection. Dengvaxia is provided as a powder in a 5-dose vial and a solvent in a 5-dose vial (2.5 mL). The powder and the solvent must be mixed together before use.

Dengvaxia is available in packs of 5 (vaccine and solvent vials provided in the same box).

The powder is a white, homogenous, freeze-dried powder with possible retraction at the base (ring-shaped cake possible).

The solvent (0.9% sodium chloride solution) is a limpid, colourless solution.

After reconstitution with the solvent provided, Dengvaxia is a clear, colourless liquid with the possible presence of white to translucent particles.

Marketing Authorisation Holder:

Sanofi Pasteur
14 Espace Henry Vallée
69007 Lyon
France

Manufacturer:

SANOFI PASTEUR
Parc Industriel d'Incarville
27100 Val de Reuil
France

Or

SANOFI PASTEUR NVL
31-33 Quai Armand Barbès
69250 Neuville-sur-Saône
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Ireland sanofi-aventis Ireland T/A SANOFI Tel: + 353 (0) 1 4035 600	Slovenija Swixx Biopharma d.o.o. Tel.: +386 1 235 51 00
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Italia Sanofi S.r.l. Tel: 800536389 Tel dall'estero: +39 02 39394983	Suomi/Finland Sanofi Oy Tel: +358 (0) 201 200 300
Κύπρος C.A. Papaellinas Ltd. Τηλ.: +357 – 22 741741	Sverige Sanofi AB Tel: +46 8-634 50 00
Latvija Swixx Biopharma SIA Tel.: +371 6 616 47 50	United Kingdom (Northern Ireland) sanofi-aventis Ireland Ltd. T/A SANOFI Tel: +44 (0) 800 035 2525

This leaflet was last revised in [{MM/YYYY}].

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

- As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in the event of an anaphylactic reaction following the administration of Dengvaxia.
- Dengvaxia must not be mixed with other medicinal products in the same syringe.
- Dengvaxia must not be administered by intravascular injection under any circumstances.
- Immunisation should be carried out by subcutaneous (SC) injection preferably in the upper arm in the region of the deltoid.
- 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.

Reconstitution and handling of multidose pack size

Dengvaxia must be reconstituted prior to administration.

Dengvaxia is reconstituted by transferring all of the solvent (0.9% sodium chloride solution) provided in the 5-dose vial with a dark gray flip-off cap into the 5-dose vial of freeze-dried powder with a medium brown flip-off cap, using a sterile syringe and needle.

1. Use a sterile syringe and needle for the transfer of the solvent.
2. Transfer the entire content of the solvent vial (with a dark gray flip-off cap) into the vial containing the powder (medium brown flip-off cap).
3. Swirl gently until the powder is dissolved.

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

After complete dissolution, a 0.5 mL dose of the reconstituted suspension is withdrawn into a sterile syringe. A new sterile syringe and needle should be used for withdrawal of each of the 5 doses. The recommended size of the needle to be used is 23G or 25G.

Before each injection, the reconstituted suspension should be gently swirled once again.

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

After reconstitution with the solvent provided, Dengvaxia must be used within 6 hours.

Partially used multidose vials must be kept between 2°C and 8°C (i.e., in a refrigerator) and protected from light.

Any remaining vaccine doses should be discarded at the end of the immunization session or within 6 hours after reconstitution, whichever comes first.

A partially used multidose vial must be discarded immediately if:

- Sterile dose withdrawal has not been fully observed.
- A new sterile syringe and needle were not used for reconstitution or withdrawal of each of the previous doses.
- There is any suspicion that the partially used vial has been contaminated.
- There is visible evidence of contamination, such as a change in appearance.

Any unused product or waste material should be disposed of in accordance with local regulations.