Attachment 1: Product information AusPAR Dengvaxia Sanofi-Aventis Australia Pty Ltd PM-2016-01679-1-2 / PM-2017-04923-1-2 / PM-2017-04924-1-2 FINAL 23 November 2018. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>

AUSTRALIAN PRODUCT INFORMATION – DENGVAXIA® POWDER AND DILUENT FOR SUSPENSION FOR INJECTION (DENGUE TETRAVALENT VACCINE (LIVE, ATTENUATED))

1 NAME OF THE MEDICINE

Dengvaxia®

Dengue tetravalent vaccine (live, attenuated)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Dengvaxia is a prophylactic, tetravalent, live attenuated viral vaccine. Each of the four CYD dengue viruses in the vaccine was obtained separately via recombinant DNA technology. The viruses were constructed by replacing the sequences encoding the pre-membrane (prM) and envelope proteins (E) of the structural proteins in the yellow fever (YF) 17D204 virus genome by those encoding for the homologous sequences of the four wild-type dengue serotypes 1 (PUO 359/TVP 1140), 2 (PUO 218), 3 (PaH881/88), and 4 (1228 – TVP 980). The immunising antigens are the prM and E proteins from dengue virus serotypes 1 to 4.

After reconstitution, one dose (0.5 mL) contains 4.5 - 6.0 $\log_{10}$ $CCID_{50}$* of each serotype of chimeric yellow fever dengue virus** (1, 2, 3 and 4).

* $CCID_{50}$: 50% Cell Culture Infectious Dose
** Produced in serum-free Vero cells by recombinant DNA technology

Contains phenylalanine. For the full list of excipients, see Section 6.1 List of excipients.

No adjuvants and no preservatives are added.

3 PHARMACEUTICAL FORM

Powder and diluent for suspension for injection

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

The diluent is a clear, colourless liquid.

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

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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 9 through 45 years of age with previous dengue infection and living in endemic areas.

Use should be in accordance with official guidelines. Previous dengue infection must be demonstrated by history of laboratory-confirmed dengue infection or serotesting according to local official recommendations.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

The primary vaccination schedule consists of 3 injections of 0.5 mL to be administered by subcutaneous injection at 6 month intervals.

If flexibility in the vaccination schedule is necessary, a time window of +/- 20 days is acceptable.

The vaccine must be used according to official guidelines. For countries considering vaccination as part of their dengue control program, WHO have recommended a 'pre-vaccination screening strategy' as the preferred option, in which only dengue-seropositive individuals are vaccinated (see Section 4.4 Special warning and precautions for use).

The need for a booster after primary vaccination with Dengvaxia has not been determined.

Administration

1. Attach the 23G x 1" (25mm) sterile needle provided to the pre-filled diluent syringe.
2. Reconstitute by transferring all of the diluent in the blue-labelled pre-filled syringe (0.4% sodium chloride solution) into the vial of freeze dried powder with a yellowish green flip-off cap.
3. Gently swirl the vial.
4. After complete dissolution, a 0.5 mL dose of the reconstituted suspension is withdrawn into the same syringe.
5. For injection, replace the 23G x 1" (25mm) needle with the 25G x 5/8" (16mm) sterile needle provided.
6. Administer by the subcutaneous injection. The recommended injection site is the deltoid region.

Do not administer by intravascular injection.

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

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

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

Dengvaxia is for single use only and must not be used in more than one individual. Discard any remaining unused contents.

4.3 CONTRAINDICATIONS

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

Dengvaxia must not be administered to individuals with a history of severe allergic reaction after prior administration of Dengvaxia.

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

Dengvaxia must not be administered to individuals with congenital or acquired immune deficiency that impairs cell-mediated immunity. This includes individuals receiving immunosuppressive therapies such as chemotherapy or high doses of systemic corticosteroids generally given for 2 weeks or more or other immunosuppressive agents (see Section 4.4 Special warnings and precautions for use).

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

Dengvaxia must not be administered to pregnant women (see Section 4.4 Special warnings and precautions for use).

Dengvaxia must not be administered to breastfeeding women (see Section 4.4 Special warnings and precautions for use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Prior to vaccination

Individuals living in non-endemic areas and visiting endemic areas should not receive the vaccine because available clinical data are not sufficient to conclude on the benefit/risk of vaccination in such individuals.

In individuals who are not immune to dengue (who have never been infected by any of the dengue virus serotype), a potential risk of virologically-confirmed dengue requiring

hospitalisation might be considered. However, current available clinical data are not sufficient to conclude on this potential risk in such individuals.

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

Before administering any biological, the person responsible for administration must take all precautions to prevent allergic or other reactions. As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in the event of an anaphylactic reaction following administration of Dengvaxia. Adrenaline (1:1000) and other appropriate agents used to control immediate allergic reactions must be available to treat unexpected events such as anaphylaxis.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to injection with a needle. Procedures should be in place to prevent injury from falling and to manage syncopal reactions.

Do not administer Dengvaxia by intravascular injection.

Protection

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

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

Individuals who have not been previously infected by dengue virus or for whom this information is unknown; in individuals who have not been previously infected by the dengue virus, an increased risk of hospitalisation for dengue and clinically severe dengue (predominantly grade 1 or 2 Dengue Hemorrhagic Fever [WHO 1997]) has been observed in the long-term follow up of clinical trials.

Vaccination should only be recommended when the potential benefits outweigh the potential risks (for those living in areas with a high dengue seroprevalence or where epidemiological data indicate a high burden of dengue disease). According to WHO, in high seroprevalence settings (> 80%) vaccination regardless of serostatus has an overall population benefit despite an increased risk for seronegative individuals. Healthcare professionals would need to assess the likelihood of prior dengue infection in individuals living in those areas before vaccinating. For individuals who have not been previously infected by dengue virus, vaccination should not be recommended. Previous infection by dengue virus has to be substantiated through serotesting where available.

In the context of WHO recommendations, in any future potential vaccination campaign in Australia, a 'pre-vaccination screening strategy' would be recommended, in which only dengue-seropositive individuals should be vaccinated.

Individuals who intend to reside in high dengue prevalence areas: Vaccination can be considered in individuals 9 through 45 years of age with laboratory-confirmed past dengue infection who can complete the full vaccination schedule over 12 months.

Travellers: Vaccination is not recommended for individuals living in non-endemic areas and travelling short term to endemic areas.

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

Phenylketonuria; Dengvaxia contains phenylalanine. It may be harmful for patients with phenylketonuria.

Fructose intolerance; Dengvaxia contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not be given this vaccine.

Use in the elderly

Dengvaxia has not been evaluated in individuals older than 60 years of age.

Paediatric use

Dengvaxia should not be administered in individuals less than 9 years of age because of concerns observed in subjects 2 to 5 years of age in the Phase III efficacy studies, regarding increased rate in vaccinated subjects of virologically-confirmed dengue disease requiring hospitalisation including clinically severe dengue in subjects with no previous dengue infection.

Effects on laboratory tests

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Concomitant administration

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

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

No specific studies have been performed on concomitant administration of Dengvaxia with any other medicinal product(s) in individuals 9 through 60 years of age living in endemic areas.

Vaccine-drug interactions

For immunosuppressive therapy or corticosteroid therapy, see Section 4.4 Special warnings and precautions for use.

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

Vaccine-vaccine interactions

Limited clinical data on sequential administration of other vaccines and Dengvaxia were collected in the early development phase. Prior administration of the following vaccines 3 to 4 months before Dengvaxia did not raise any safety concerns;

- Typhoid vaccine (42 subjects 2 through 45 years of age) or
- Inactivated Japanese encephalitis vaccine (32 subjects 18 through 45 years of age) or
- Yellow fever vaccine (42 subjects 2 through 45 years of age)

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No specific studies have been performed on fertility.

Repeated exposure of female rabbits to the clinical dose of Dengvaxia by intravenous injection, 30 and 10 days prior to mating showed no effects on female mating or fertility.

Use in pregnancy

Category B2

Dengvaxia must not be administered to pregnant women (see Section 4.3 Contraindications).

Women of childbearing age should be advised not to become pregnant for 4 weeks after receiving any injection of Dengvaxia.

No specific studies have been performed on the vaccine in pregnant women. Cases of inadvertent exposure during pregnancy were reported during clinical studies. These data are

not sufficient to conclude on the absence of potential effects of Dengvaxia on pregnancy, embryo-fetal development, parturition and post-natal development.

No adverse effects on embryofetal development were observed in female mice injected with the clinical dose of Dengvaxia (approximately 5 log10 CCID50 per serotype) on gestation day 6, 9 or 12. Increases in post-implantation loss, reduced fetal bodyweights, and reduced fetal ossification were observed at a higher dose (approximately 6.5 or 8 log10 CCID50 per serotype) but were associated with maternal toxicity (reduced bodyweight gains and food consumption). Maternal exposure to virus was only detected at the high-dose, none was detected in fetuses. Serum neutralising antibodies against vaccine serotypes were detected in some dams and pups at all doses.

Female New Zealand White rabbits injected intravenously with the clinical dose of Dengvaxia (approximately 5 log10 CCID50 per serotype), 30 and 10 days before mating and on gestation days 6, 12 and 27, showed no adverse effects on embryofetal or postnatal development. Neutralising antibodies against all vaccine serotypes were detected in all rabbits and were transferred to all fetuses and pups.

Use in lactation

Dengvaxia must not be administered to breastfeeding women (see Section 4.3 Contraindications).

It is not known whether Dengvaxia is excreted into human milk. No studies have been performed on the effect on breastfed infants of administration of Dengvaxia to their mothers.

Female mice injected with a single intravenous dose of Dengvaxia (approximately 5, 6.5 or 8 log10 CCID50 per serotype) on day 14 of lactation showed a transient bodyweight loss at the medium- dose and high-dose, but there were no adverse effects on pups. Virus was detected in the serum of a minority of mice at the high-dose only, but was not detected in the milk of lactating mice or in the serum of pups. Dengue virus antibodies were detected in some dams and pups.

Female New Zealand White rabbits were injected intravenously with the clinical dose of Dengvaxia (approximately 5 log10 CCID50 per serotype), 30 and 10 days before mating and on gestation days 6, 12 and 27. There were no adverse effects on the pups. Neutralising antibodies against all vaccine serotypes were detected in all dams and pups.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials Experience

A total of approximately 28,500 subjects 9 months through 60 years of age received at least one injection of the final formulation of Dengvaxia, irrespective of the vaccination schedule, in completed or ongoing Phase I to Phase III clinical studies, including the 2 ongoing large-scale efficacy studies, CYD14 and CYD15.

Data in subjects 9 years of age or older

Among these 28,500 subjects, approximately 20,667 subjects aged 9 through 60 years received at least one injection of the final formulation of Dengvaxia according to the claimed vaccination schedule in 13 randomised, observer-blinded, placebo-controlled Phase II to Phase III clinical studies.

The safety profile presented below is based on a pooled analysis including a total of 1547 subjects 18 through 60 years of age and 19,120 subjects 9 through 17 years of age. Reactogenicity was assessed in a subset of 4615 subjects, including 1547 subjects 18 through 60 years of age and 3068 subjects 9 through 17 years of age.

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

In subjects 9 through 60 years of age, the most frequently reported ARs following any injection of Dengvaxia were headache, injection site pain, malaise and myalgia.

The adverse reactions (ARs) were usually mild to moderate in severity and of short duration (0 to 3 days). Onset was typically observed 0 to 3 days after the injection of Dengvaxia, except for fever which appeared throughout the solicited period, i.e. up to 14 days after the injection.

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

ARs are listed according to the following frequency categories:

Very common ≥ 1/10 (≥ 10%),

Common ≥ 1/100 to < 1/10 (≥ 1% and < 10%),

Uncommon ≥ 1/1000 to < 1/100 (≥ 0.1% and < 1%),

Rare ≥ 1/10,000 to < 1/1000 (≥ 0.01% and < 0.1%) and

Very rare < 1/10,000 (< 0.01%).

The database allowed for the detection of very common, common and uncommon Adverse Events (AEs).

Table 1 (above 18 years of age) and Table 2 (below 18 years of age) below summarise the AEs reported within 28 days after any injection, with a frequency ≥ 1.0% and which were assessed as having a reasonable possibility that the AE was caused by the product administered during clinical studies (referred to as 'Related Adverse Events').

Table 1 - Related Adverse Events (≥ 1.0%) reported within 28 days in adults subjects (above 18 years of age) after any injection of Dengvaxia or the placebo

	Dengvaxia		Placebo	
Adverse Events	**n/M**	**%**	**n/M**	**%**
Headache	784/1524	51.4	81/299	27.1
Injection site Pain	689/1524	45.2	43/299	14.4
Malaise	675/1524	44.3	66/299	22.1
Myalgia	643/1524	42.2	58/299	19.4
Asthenia	432/1524	28.3	35/299	11.7
Injection site Erythema	120/1524	7.9	0/299	0.0
Fever	75/1522	4.9	4/299	1.3
Injection site swelling	37/1524	2.4	1/299	0.3
	n/N	%	n/N	%
Injection site haematoma	45/1547	2.9	6/302	2.0
Injection site pruritus	23/1547	1.5	0/302	0.0%

n: number of subjects experiencing the endpoint
N: total number of subjects per dose
M: number of subjects with available data for the relevant endpoint/ solicited adverse events reported within 7 days for injection site reactions and within 14 days for systemic reactions

Table 2 - Related Adverse Events (≥ 1.0%) reported within 28 days in paediatric subjects below 18 years of age after any injection of Dengvaxia or the placebo

	Dengvaxia		Placebo	
Adverse Events	**n/M**	**%**	**n/M**	**%**
Headache	1649/3048	54.1	762/1471	51.8
Injection site Pain	1502/3050	49.2	574/1470	39.0
Myalgia	1280/3047	42.0	560/1471	38.1
Malaise	1247/3047	40.9	552/1471	37.5
Asthenia	1042/3047	34.2	460/1471	31.3
Fever	500/3040	16.4	228/1465	15.6
Injection site Erythema	255/3049	8.4	110/1470	7.5
Injection site swelling	209/3050	6.9	75/1470	5.1

n: number of subjects experiencing the endpoint
M: number of subjects with available data for the relevant endpoint/ solicited adverse events reported within 7 days for injection site reactions and within 14 days for systemic reactions
Injection site haematoma and pruritus were reported in subjects 9 through 17 years of age with a frequency uncommon

The following ARs were reported during clinical studies in subjects 9 through 60 years of age within 28 days after injection of Dengvaxia with a frequency uncommon:

Infections and infestations:

- Upper respiratory tract infection

Blood and lymphatic tissue disorders:

- Lymphadenopathy

Nervous system disorders:

- Dizziness, migraine

Respiratory, thoracic and mediastinal disorders:

- Oropharyngeal pain, cough, rhinorrhoea

Gastrointestinal disorders:

- Nausea

Skin and subcutaneous tissue disorders:

- Rash, urticaria

Musculoskeletal and connective tissue disorders:

- Neck pain, arthralgia

General disorders and administration site conditions:

- Injection site induration, influenza-like illness

Few of these uncommon ARs were observed with the following age-group specificities:

- Lymphadenopathy, migraine, arthralgia and influenza-like illness were only reported in subjects 18 through 60 years of age;
- Urticaria was only reported in subjects 9 through 17 years of age;
- Upper respiratory tract infection, dizziness, oropharyngeal pain, cough, rhinorrhoea, nausea, rash and neck pain were less frequently reported in subjects 9 through 17 years of age (frequency: rare or very rare, i.e., with a frequency < 0.1%).

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

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

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

Adverse Reactions from Post-Marketing Surveillance

Based on spontaneous reporting, the following additional adverse events have been reported after commercial use. These events have been very rarely reported, however exact incidence rates cannot be calculated precisely.

Immune system disorders

- Allergic including anaphylactic reactions

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No cases of overdose have been reported in clinical studies with Dengvaxia.

For general advice on overdose management, contact the Poisons Information Centre, telephone number 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC code: J07BX

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

Mechanism of action

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

Clinical trials

Immunogenicity

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

During clinical development, immunogenicity data were collected in a total of approximately 5700 subjects 9 months through 60 years of age that received at least one injection of the vaccine.

Among these 5700 subjects, a total of approximately 3104 subjects 9 through 45 years of age from endemic areas received at least one injection of the final formulation of Dengvaxia according to the claimed vaccination schedule in 10 randomised, observer-blinded, placebo-

controlled Phase II to Phase III clinical studies. Most of the subjects were 9 through 17 years of age (n= 2810).

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

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

				Serotype 1			Serotype 2			Serotype 3			Serotype 4	
Age group	**Region**	**Study**	**N**	**Pre-injection 1 GM (95% CI)**	**Post-injection 3 GM (95% CI)**	**N**	**Pre-injection 1 GM (95% CI)**	**Post-injection 3 GM (95% CI)**	**N**	**Pre-injection 1 GM (95% CI)**	**Post-injection 3 GM (95% CI)**	**N**	**Pre-injection 1 GM (95% CI)**	**Post-injection 3 GM (95% CI)**
Subjects 18 through 45 years of age	**Endemic Asia Pacific**	**CYD22**	20	327 (148; 725)	695 (335; 1443)	20	350 (168; 730)	825 (493; 1383)	20	160 (87.5; 291)	424 (286; 627)	20	75.0 (35.0; 161)	375 (251; 561)
		CYD28	148	15.8 (11.7; 21.5)	48.7 (33.6; 70.4)	148	16.9 (12.3; 23.1)	66.9 (47.9; 93.5)	148	14.5 (11.2; 18.7)	88.4 (68.6; 114)	148	10.1 (8.03; 12.7)	122 (96.5; 155)
		CYD47	126	184 (127; 268)	461 (340; 625)	126	204 (141; 294)	484 (370; 634)	126	219 (153; 312)	709 (552; 911)	126	55.4 (41.4; 74.2)	336 (271; 417)
Subjects 9 through 17 years of age	**Endemic Asia Pacific**	**CYD14**	615	79.5 (65.9; 96.0)	255 (217; 299)	615	133 (111; 159)	530 (469; 600)	615	77.0 (64.6; 91.8)	289 (253; 331)	615	46.3 (39.8; 53.8)	201 (181; 223)
		CYD23	73	98.8 (54.9; 178)	276 (162; 471)	73	123 (69.4; 217)	490 (333; 721)	73	61.2 (37.5; 100)	457 (320; 651)	73	45.8 (29.1; 72.0)	197 (157; 249)
	Endemic Latin America	**CYD15**	1301	128 (112; 145)	395 (353; 441)	1301	138 (123; 156)	574 (528; 624)	1301	121 (108; 136)	508 (465; 555)	1301	43.6 (39.6; 48.0)	241 (226; 258)

The lower limit of quantification for dengue neutralising antibodies is 10 (1/dil).
Endemic areas are defined as areas where the disease has been continuously present in the native population with documented outbreaks or epidemics.
CYD22: Vietnam; CYD28: Singapore; CYD47: India; CYD14: Indonesia, Malaysia, the Philippines, Thailand, Vietnam; CYD23: Thailand; CYD15: Brazil, Colombia, Honduras, Mexico, Puerto Rico.

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

Differences in GMTs 28 days after the third injection were observed depending on dengue immune status[1] before the first injection, the age and the region. Overall:

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

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

Data on long-term persistence of antibodies

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

Efficacy

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

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

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

The efficacy of Dengvaxia against severe VCD cases and against hospitalised VCD cases (i.e., hospital admission due to dengue, whatever the severity) were also evaluated. For severe VCD cases, two types of endpoints were considered: clinically severe VCD cases and VCD

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

cases that met WHO criteria for Dengue Haemorrhagic Fever (DHF). Vaccine efficacy was demonstrated for these three endpoints in both studies and in the meta-analysis.

The efficacy results were also analysed according to covariates, i.e., age at the time of the first injection and dengue immune status before the first injection. In subjects 9 through 16 years of age, no significant effect of age on vaccine efficacy was observed, while a higher efficacy against VCD (any serotype and any severity) was observed in subjects with prior dengue infection (i.e. subjects with neutralising antibodies against any of the 4 dengue serotypes prior vaccination) compared to the overall population. In CYD14 and CYD15, combined vaccine efficacy was 81.9% (95% CI: 61.7; 90) for any serotype in subjects with prior dengue infection (i.e. subjects with neutralising antibodies against any of the 4 dengue serotypes prior vaccination) compared to 65.6% (95% CI: 60.7; 69.9) for the overall population (see Table 4).

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

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

	CYD14 VE % (95%CI)*	CYD15 VE % (95%CI)*	CYD14+CYD15 VE % (95%CI)*
Any serotype	67.8 (57.7; 75.6)	64.7 (58.7; 69.8)	65.6 (60.7; 69.9)
Serotype 1	65.7 (46.6; 78.2)	54.8 (40.2; 65.9)	58.4 (47.7; 66.9)
Serotype 2	36.8 (-10.1; 63.3)	50.2 (31.8; 63.6)	47.1 (31.3; 59.2)
Serotype 3	69.5 (31.9; 87.0)	74.2 (63.9; 81.7)	73.6 (64.4; 80.4)
Serotype 4	87.9 (75.5; 94.6)	80.9 (70.9; 87.7)	83.2 (76.2; 88.2)
Clinically severe VCD cases	90.9 (58.4; 99.0)	95.5 (68.8; 99.9)	93.2 (77.3; 98.0)
DHF meeting any WHO criteria	90.9 (58.4; 99.0)	95.0 (64.9; 99.9)	92.9 (76.1; 97.9)
Hospitalised VCD	81.6 (60.7; 92.0)	80.3 (64.7; 89.5)	80.8 (70.1; 87.7)
VCD any serotype in subjects with neutralising antibodies against dengue prior vaccination **	79.2 (47.2; 92.7)	83.7 (62.2; 93.7)	81.9 (67.2; 90.0)

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

- Subjects with quantified (≥ 10 [1/dil], the lower limit of quantitation) neutralising antibodies against at least one dengue serotype in the baseline sample.

Bridging of efficacy data to individuals 17 through 45 years of age in endemic areas

The 2 pivotal efficacy studies showed that higher post-injection 3 GMTs were associated with higher protection.

Based on immunogenicity data from Phase II studies conducted in Asia (CYD22 conducted in Vietnam in 180 subjects 2 through 45 years of age including 30 adults, and CYD47, conducted in India in 189 subjects 18 through 45 years of age), similar or higher neutralising antibody levels after the third injection are anticipated in adults from endemic areas, and thus a similar or higher level of protection after the third injection of the vaccine is expected in individuals 17 through 45 years of age in endemic areas compared to the vaccine efficacy observed in the CYD14 and CYD15 studies.

Data from a Phase III study conducted in non-endemic areas (CYD17, conducted in Australia in 715 subjects 18 through 60 years of age including 241 subjects above 45 years of age) showed that the immunogenicity profile of the individuals 46 through 60 years of age is similar to the one of the individuals 18 through 45 years of age in the same region.

5.2 PHARMACOKINETIC PROPERTIES

No pharmacokinetic studies have been performed on Dengvaxia.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Dengvaxia has not been evaluated for genotoxic potential.

Carcinogenicity

Dengvaxia has not been evaluated for carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Powder:

Essential amino acids (cystine, tyrosine, arginine hydrochloride, histidine, isoleucine, leucine, lysine hydrochloride, methionine, phenylalanine, threonine, tryptophan and valine)

Non-essential amino acids (alanine, asparagine, aspartic acid, glutamic acid, proline, serine and glycine)

Arginine hydrochloride

Sucrose

Trehalose dihydrate

Sorbitol

Trometamol

Urea

Diluent:

Sodium chloride

Water for injection

6.2 INCOMPATIBILITIES

Dengvaxia must not be mixed with any other injectable vaccine(s) or medicinal product(s), see Section 4.5 Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

36 months

Dengvaxia should be used immediately after reconstitution with the diluent provided. However, in-use stability studies showed that the reconstituted product can be kept for up to 6 hours at 2°C to 8°C (i.e., in a refrigerator).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2°C–8°C). Do not freeze. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Dengvaxia is supplied in:

- Powder (1 dose) in vial + 0.5 mL of diluent in a pre-filled syringe with 2 separate needles

Pack size of 1 or 10. Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

After use, any remaining vaccine and container must be disposed of safely, preferably by heat inactivation or incineration, according to locally agreed procedures.

6.7 PHYSICOCHEMICAL PROPERTIES

Not applicable

Attachment 1: Product information AusPAR Dengvaxia Sanofi-Aventis Australia Pty Ltd PM-2016-01679-1-2 / PM-2017-04923-1-2 / PM-2017-04924-1-2 FINAL 23 November 2018. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113
Australia
Tel: 1800 818 806

9 DATE OF FIRST APPROVAL

20 July 2017

10 DATE OF REVISION

06 September 2018

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.1	Amended indication to include confirmation on seropositivity prior to vaccination
4.2	Addition of WHO recommendations
4.4	Addition of WHO recommendations and associated precautions
4.7	Statement on the ability to drive or to use machines added
4.8	Heading added for clarity, long-term safety follow-up data updated
5.1	Addition of pharmacotherapeutic group and ATC details. Clinical trials section updated to remove the terms “immune subjects” and “non-immune subjects”.
5.2	Statement on pharmacokinetic studies added
6.6	Special precautions for disposal added
8	Change of Sponsor contact phone number