HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DENGVAXIA safely and effectively. See full prescribing information for DENGVAXIA.

DENGVAXIA (Dengue Tetravalent Vaccine, Live)
Suspension for Subcutaneous Injection
Initial U.S. Approval: 2019

----------INDICATIONS AND USAGE----------
DENGVAXIA is a vaccine indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4. DENGVAXIA is approved for use in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.

Limitations of use:

- DENGVAXIA is not approved for use in individuals not previously infected by any dengue virus serotype or for whom this information is unknown. Those not previously infected are at increased risk for severe dengue disease when vaccinated and subsequently infected with dengue virus. (5.1) Previous dengue infection can be assessed through a medical record of a previous laboratory-confirmed dengue infection or through serological testing prior to vaccination. (1)
- The safety and effectiveness of DENGVAXIA have not been established in individuals living in dengue non-endemic areas who travel to dengue endemic areas. (1)

----------DOSAGE AND ADMINISTRATION----------
Three doses (0.5 mL each) 6 months apart (at month 0, 6, and 12). (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Suspension for injection (0.5 mL) supplied as a lyophilized powder to be reconstituted with the supplied diluent. (3)

----------CONTRAINDICATIONS----------
- A history of severe allergic reaction to a previous dose of DENGVAXIA or to any component of DENGVAXIA. (4.1)
- Immunocompromised individuals. (4.2)

----------WARNINGS AND PRECAUTIONS----------
- In persons not previously infected by dengue virus, an increased risk of severe dengue disease can occur following vaccination with DENGVAXIA and subsequent infection with any dengue virus serotype. (5.1)
- There is no FDA-cleared test available to determine a previous dengue infection. (5.1)

----------ADVERSE REACTIONS----------
The most frequently reported adverse reactions regardless of the dengue serostatus prior to vaccination were headache (40%), injection site pain (32%), malaise (25%), asthenia (25%) and myalgia (29%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 or http://vaers.hhs.gov.

----------DRUG INTERACTIONS----------
False negative tuberculin purified protein derivative (PPD) test results may occur within 1 month following vaccination with DENGVAXIA. (7.3)

See **17 for PATIENT COUNSELING INFORMATION**

Revised: [5/2019]

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DENGVAXIA® (Dengue Tetravalent Vaccine, Live) is a vaccine indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4. DENGVAXIA is approved for use in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.

Limitations of use

- DENGVAXIA is not approved for use in individuals not previously infected by any dengue virus serotype or for whom this information is unknown. Those not previously infected are at increased risk for severe dengue disease when vaccinated and subsequently infected with dengue virus. *[See Warnings and Precautions (5.1).]* Previous dengue infection can be assessed through a medical record of a previous laboratory-confirmed dengue infection or through serological testing prior to vaccination.
- The safety and effectiveness of DENGVAXIA have not been established in individuals living in dengue non-endemic areas who travel to dengue endemic areas.

2 DOSAGE AND ADMINISTRATION

For subcutaneous use only.

2.1 Dose

Three doses (0.5 mL each) 6 months apart (at month 0, 6, and 12).

2.2 Preparation

The package contains a vial of lyophilized vaccine antigen and a vial of saline diluent (0.4% NaCl).

After removing the “flip-off” caps, cleanse the lyophilized vaccine antigen and diluent vial stoppers with a suitable germicide. Do not remove the vial stoppers or metal seals holding them in place.

To reconstitute DENGVAXIA, use a sterile needle and syringe to withdraw 0.6 mL from the diluent vial and inject it into the vial of the lyophilized vaccine antigen. Swirl the vial gently.

Changing needles between withdrawing the vaccine from the vial and injecting it into a recipient is not necessary unless the needle has been damaged or contaminated.

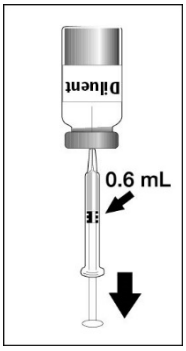	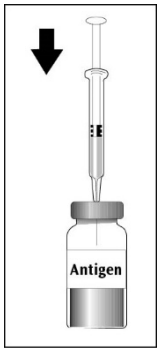	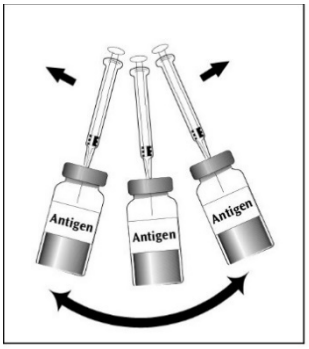	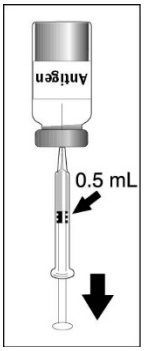
Figure 1 Insert the syringe needle through the stopper of the vial of diluent and withdraw 0.6 mL liquid content.	**Figure 2** Insert the syringe needle through the stopper of the vial of lyophilized vaccine antigen and inject the liquid into the vial.	**Figure 3** Swirl vial gently. The syringe needle is not removed while swirling the vial.	**Figure 4** After reconstitution, withdraw 0.5 mL. DENGVAXIA should be used immediately after reconstitution.

After reconstitution, the suspension is colorless and may develop trace amounts of white to translucent endogenous proteinaceous particles. *[See Description (11).]*

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard the vial if the solution is cloudy or contains particles other than trace amounts of white to translucent particles.

Discard reconstituted vaccine if not used within 30 minutes. *[See How Supplied/Storage and Handling (16.2).]*

DENGVAXIA should not be mixed in the same syringe with other parenteral products.

2.3 Administration

After reconstitution, withdraw 0.5 mL of DENGVAXIA and administer subcutaneously immediately or store refrigerated at 2°C to 8°C (36°F to 46°F) and use within 30 minutes. Do not administer DENGVAXIA by intramuscular injection.

3 DOSAGE FORMS AND STRENGTHS

DENGVAXIA is a suspension for injection (supplied as a lyophilized powder to be reconstituted with the supplied diluent, 0.4% NaCl). A single dose, after reconstitution, is 0.5 mL.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Do not administer DENGVAXIA to individuals with a history of severe allergic reaction to a previous dose of DENGVAXIA or to any component of DENGVAXIA. *[See Description (11).]*

4.2 Immunocompromised Individuals

Do not administer DENGVAXIA to individuals with severe immunodeficiency or immunosuppression due to disease or therapy.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Severe Dengue Disease Following DENGVAXIA in Persons not Previously Infected with Dengue Virus

In unvaccinated individuals, first dengue infections rarely cause severe dengue, while second dengue infections with a different serotype are associated with an increased risk of severe dengue. DENGVAXIA administration to individuals not previously infected by dengue virus is associated with an increased risk of severe dengue disease when the vaccinated individual is subsequently infected with any dengue virus serotype. Therefore, healthcare professionals must evaluate individuals for prior dengue infection to avoid vaccinating individuals who have not been previously infected by dengue virus.

Previous infection by dengue virus can be evaluated through a medical record of previous laboratory-confirmed dengue infection or through serotesting prior to vaccination.

There is no FDA cleared test available to determine a previous dengue infection. Available non-FDA cleared tests may yield false positive results (e.g., due to cross-reactivity with other flaviviruses).

5.2 Management of Acute Allergic Reactions

DENGVAXIA may cause hypersensitivity reactions, including anaphylaxis. Appropriate medical treatment and supervision must be available following administration of DENGVAXIA.

5.3 Limitations of Vaccine Effectiveness

Vaccination with DENGVAXIA may not protect all individuals. It is recommended to continue personal protection measures against mosquito bites after vaccination.

5.4 Syncope

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

The safety of DENGVAXIA in subjects 9 through 16 years of age was evaluated in 9 randomized, placebo-controlled, multicenter clinical trials. In these studies, a total of 19,102 subjects 9 through 16 years of age received at least one dose of DENGVAXIA and 9,484 received placebo (0.9% sodium chloride). Overall, 50.9% of trial participants who received DENGVAXIA or placebo were female. Racial groups were reported as 18.9% Asian, 13% American Indian or Alaska native, 6.4% caucasian, 2.6% black, and 59.1% as other. In the largest study (Study 1, NCT01374516; N = 20,869) conducted in four Latin American countries and Puerto Rico, most subjects (99.9%) reported Hispanic ethnicity. All studies enrolled subjects irrespective of evidence of previous dengue infection.

Solicited Adverse Reactions

In a multi-center, observer-blind, randomized (2:1), placebo-controlled trial conducted in four Latin American countries and Puerto Rico (Study 1, NCT01374516), 2,000 subjects (out of a total of 20,869 subjects) were recruited during the first 2 months of enrollment for inclusion in the reactogenicity subset. Solicited adverse reactions were recorded daily for 14 days following each vaccination.

Table 1 presents the frequency and severity of solicited injection site reactions reported within 7 days and systemic adverse reactions reported within 14 days following receipt of DENGVAXIA or placebo.

Table 1: Percentages of Subjects with Solicited Injection Site Reactions within 7 Days and Systemic Adverse Reactions within 14 Days Following Receipt of Each Dose of DENGVAXIA or Placebo in Children and Adolescents 9 through 16 Years of Age in Study 1

		Dose 1		Dose 2		Dose 3	
		DENGVAXIA % N = 1,264-1,326	Placebo % N = 635-657	DENGVAXIA % N = 1,228-1,298	Placebo % N = 594-639	DENGVAXIA % N = 1,215-1,279	Placebo % N = 597 -631
Injection Site Reactions							
Pain[*]	Any	32.4	26.3	25.6	16.4	22.5	16.5
	Grade 3	0.8	0.9	0.5	0.0	0.9	0.3
Erythema[†]	Any	4.1	4.7	1.9	1.7	1.5	1.6
	Grade 3	0.0	0.2	<0.1	0.0	0.0	0.0
Swelling[†]	Any	3.5	2.7	1.9	0.9	1.6	1.3
	Grade 3	0.0	0.2	0.0	0.0	0.0	0.0
Systemic Adverse Reactions							
Asthenia[‡]	Any	24.6	22.5	17.8	16.4	16.3	17.4
	Grade 3	2.7	2.6	1.8	1.1	1.3	1.3
Fever[§]	Any	6.8	6.6	5.9	7.1	7.3	8.7
	Grade 3	1.7	1.1	0.8	1.2	1.1	0.8
Headache[‡]	Any	39.9	41.6	29.8	28.5	29.6	25.0
	Grade 3	5.1	4.1	2.1	2.3	2.6	1.9
Malaise[‡]	Any	24.5	25.9	20.8	16.6	19.3	15.2
	Grade 3	2.4	2.3	1.3	1.3	1.4	1.1
Myalgia[‡]	Any	29.2	27.4	21.0	15.8	20.0	18.4
	Grade 3	2.2	1.5	1.6	0.8	1.5	0.8

N: range number of subjects with available data for the specified endpoints
Study 1, NCT01374516
Placebo: 0.9% sodium chloride
[*] For subjects 9 through 11 years of age – Grade 3: Incapacitating, unable to perform usual activities. For subjects 12 through 16 years of age – Grade 3: Significant; prevents daily activity.
[†] For subjects 9 through 11 years of age – Grade 3: ≥50 mm. For subjects 12 through 16 years of age – Grade 3: >100 mm.
[‡] For all subjects – Grade 3: Significant; prevents daily activity.
[§] For all subjects – Any Fever: ≥38.0°C. Grade 3: ≥39.0°C.

Unsolicited Non-Serious Adverse Reactions

In Study 1, 1.2% of subjects in the DENGVAXIA group (16/1,333) and 0.8% of subjects in the placebo group (5/664) reported at least 1 unsolicited non-serious adverse reaction within 28 days following any dose.

In this study, 0.7% of the subjects in the DENGVAXIA group and 0.5% in the placebo group reported at least one unsolicited non-serious injection site adverse reaction. The unsolicited non-serious adverse reactions were injection site pain, hematoma, pruritus and anesthesia in the vaccine group and pain and induration in the control group.

In this study, 0.5% of the subjects in the DENGVAXIA group and 0.3% in the placebo group reported at least one unsolicited non-serious systemic adverse reaction. The unsolicited non-serious systemic adverse reactions were malaise, abdominal pain, vomiting, dyspnea, generalized erythema, vertigo, asthma crisis and urticaria in the vaccine group and pruritus and lymphadenitis in the control group.

Most unsolicited non-serious adverse reactions started within 3 days of any injection and resolved within 3 days or less.

A total of 2 subjects (one subject with asthma crisis and urticaria occurring the day of the first dose, and one subject with malaise occurring 20 days after the first dose) in the DENGVAXIA group (0.2%) and none in the placebo group reported unsolicited non-serious Grade 3 (significant; prevents daily activity) adverse reactions.

Severe Dengue Following Vaccination with DENGVAXIA and Subsequent Dengue Infection

Subjects were monitored for severe dengue from Day 0 (day of first study vaccination) to Month 60-72 (after first study vaccination) in three multi-center, observer-blind, randomized (2:1), placebo-controlled trials conducted in Latin America and Puerto Rico (Study 1, NCT01374516) and the Asia-Pacific region (Study 2, NCT01373281; Study 3, NCT00842530). A subset of 3,203 subjects (80.1%) enrolled in Study 3 were reconsented to participate in an extension study to evaluate safety of DENGVAXIA for 72 months (Study 4, NCT01983553). A total of 18,265 children and adolescents 9 through 16 years of age enrolled in these trials received at least one dose of DENGVAXIA. Table 2 presents the incidences and hazard ratios of severe dengue from Month 13 to Month 60-72 post-vaccination with DENGVAXIA or placebo in children and adolescents 9 through 16 years of age, by dengue baseline serostatus. An increased rate of severe dengue was observed following vaccination with DENGVAXIA and subsequent infection with any dengue virus serotype in persons not previously infected by dengue virus. *[See Warnings and Precautions (5.1).]*

Table 2: Number of Events and Incidence of Severe Dengue* From Month 13 to Month 60-72† in Children 9 through 16 Years of Age, by Previous Dengue Infection Status, in Studies 1, 2, 3 and 4

Dengue Infection Status at Month 13‡	**DENGVAXIA n (Incidence§, %)**	**Placebo n (Incidence§, %)**	**Hazard Ratio of Severe Dengue (95% CI)**
Previous Dengue Infection (Dengue sero-positive at Month 13)	10 (0.068)	27 (0.401)	0.18 (0.09; 0.37)
No Previous Dengue Infection (Dengue sero-negative at Month 13)	12 (0.380)	1 (0.069)	6.25 (0.81; 48.32)

n: number of subject with severe dengue cases
CI: confidence interval
Study 1, NCT01374516; Study 2, NCT01373281; Study 3, NCT00842530; Study 4, NCT01983553

* Severe Dengue according to IDMC (Independent Data Monitoring Committee) definition: Proven dengue fever (2 days fever + virological confirmation) plus one of the following: (a) Platelet count ≤100,000/µL and bleeding plus plasma leakage (effusion on chest x-ray [CXR] or clinically apparent ascites including imaging procedures or hematocrit ≥20% above baseline recovery level or standard for age if only one reading); (b) shock; (c) bleeding (requiring blood transfusion); (d) encephalopathy; (e) liver impairment; (f) impaired kidney function; (g) myocarditis, pericarditis or clinical heart failure.

† The follow-up period corresponded to a minimum of 60 months for Study 1, a minimum of 63 months for Study 2 and 72 months for the combination of Study 3 and its extension, Study 4.

‡ Based on measured Dengue anti-NS1 IgG ELISA at Month 13 from first vaccination (Dengue Seropositive= ≥9EU/mL).

§ Cumulative incidence over 4 years from 13 months after the first vaccination.

Non-Fatal Serious Adverse Events

In the 9 studies conducted among subjects 9 through 16 years of age (NCT 01374516, NCT01373281, NCT00842530, NCT00993447, NCT00875524, NCT00788151, NCT00880893, NCT01187433, NCT01254422), subjects were monitored for serious adverse events (SAEs) for at least 6 months after the last dose of DENGVAXIA.

The proportions of subjects who reported at least 1 non-fatal SAE within 28 days following any dose were 0.6% (123/19,102) in the DENGVAXIA group and 0.8% (73/9,484) in the placebo group. The following events were considered related to DENGVAXIA: asthma attack (day of Dose 1), urticaria (day of Dose 2) and convulsion (day of Dose 1).

The proportions of subjects who reported at least 1 non-fatal SAE after 28 days and up to 6 months after any dose were similar in the 2 groups: 2.8% in the DENGVAXIA group (534/19,102) and 3.2% in the placebo group (307/9,484). None of these SAEs were considered related to the vaccination.

Deaths

From the first administered dose up to Month 72, 51 deaths (0.3%) for subjects who received DENGVAXIA and 26 deaths (0.3 %) for subjects who received placebo were reported in the 9 studies conducted among subjects 9 though 16 years of age. None of the deaths were considered related to vaccination. Causes of death among subjects were consistent with those generally reported in children and adolescent populations.

6.2 Data from Post-marketing Experience

In addition to events reported in clinical trials for DENGVAXIA, the following adverse events

have been spontaneously reported during post-approval use. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

The following adverse events were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to DENGVAXIA.

Immune system disorders

Allergic including anaphylactic reactions.

Infections and infestations

Severe dengue infection, including hospitalization and death, in individuals for whom dengue infection status prior to vaccination was unknown and who were subsequently infected with dengue following vaccination.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

Data are not available to establish the safety and immunogenicity of concomitant administration of DENGVAXIA with recommended adolescent vaccines.

7.2 Immunosuppressive Treatments

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to DENGVAXIA.

7.3 Drug/Laboratory Test Interactions

DENGVAXIA may cause temporary depression of tuberculin purified protein derivative (PPD) test sensitivity, leading to false negative results. Tuberculin testing should be performed before DENGVAXIA is administered or at least 1 month following vaccination with DENGVAXIA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DENGVAXIA during pregnancy. Women who receive DENGVAXIA during pregnancy are encouraged to contact directly, or have their healthcare professional contact, Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE) to enroll in or obtain information about the registry.

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

No specific studies of DENGVAXIA have been performed among pregnant women. A limited number of cases of inadvertent exposure during pregnancy were reported during clinical studies. Isolated adverse pregnancy outcomes (e.g., stillbirth, intrauterine death, spontaneous abortion, blighted ovum) have been observed for these exposed pregnancies, with similar frequency and nature in the vaccinated individuals compared to the control group, and with risk factors identified for all cases. Available data in pregnant women are not sufficient to determine the effects of DENGVAXIA on pregnancy, embryo-fetal development, parturition and post-natal development.

In two developmental toxicity studies, the effect of DENGVAXIA on embryo-fetal and post-natal development was evaluated in pregnant rabbits and mice. A developmental toxicity study was performed in female rabbits given a 5 $\log_{10}$ 50% cell culture infectious dose ($CCID_{50}$) of DENGVAXIA (full human dose ranging from 4.5 $\log_{10}$ to 6.0 $\log_{10}$ $CCID_{50}$) by intravenous injection prior to mating and during gestation. The study revealed no evidence of harm to the fetus due to DENGVAXIA. In another study, female mice were administered a single dose of 5 $\log_{10}$ $CCID_{50}$, 6.5 $\log_{10}$ $CCID_{50}$ (about 3 times the highest human dose) or 8 $\log_{10}$ $CCID_{50}$ (about 100 times the highest human dose) of DENGVAXIA by intravenous injection during gestation. Fetal toxicities were observed at maternally toxic doses. *[See Animal Data (8.1).]*

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Pregnant women are at increased risk of complications associated with dengue infection compared to non-pregnant women. Pregnant women with dengue may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery. Vertical transmission of dengue virus from mothers with viremia at delivery to their infants has been reported.

Fetal/neonatal adverse reactions

Vaccine viremia can occur 7 to 14 days after vaccination with a duration of <7 days *[See Pharmacokinetics (12.3).]*. The potential for transmission of the vaccine virus from mother to infant is unknown.

Animal Data

In two developmental toxicity studies, the effect of DENGVAXIA on embryo-fetal and post-natal development was evaluated in pregnant rabbits and mice.

Rabbits were administered a full human dose [0.5 mL (5 $\log_{10}$ $CCID_{50}$/animal/occasion)] of DENGVAXIA by intravenous injection 30 and 10 days before mating and on Days 6, 12 and 27 during gestation. No vaccine-related fetal malformation or variations and adverse effects on female fertility or pre-weaning development were reported in this study. Pregnant mice were administered a single dose of either 5 $\log_{10}$ $CCID_{50}$ (full human dose ranging from 4.5 $\log_{10}$ to

6.0 log_{10} $CCID_{50}$), 6.5 log_{10} $CCID_{50}$ (about 3 times the highest human dose) or 8 log_{10} $CCID_{50}$ (about 100 times the highest human dose) of DENGVAXIA by intravenous injection on Day 6, 9 or 12 of gestation. At doses of 6.5 log_{10} $CCID_{50}$ or 8 log_{10} $CCID_{50}$ of DENGVAXIA, maternal toxicity was observed which was associated with increased post-implantation loss and at doses of 8 log_{10} $CCID_{50}$ with reduced fetal body weight. The significance of this observation for humans is unknown, especially considering the different route of administration (the human route of administration is subcutaneous) and dose levels which exceeded the intended human dose. There were no vaccine related fetal malformations or other evidence of teratogenesis noted in this study.

8.2 Lactation

Risk Summary

Human data are not available to assess the impact of DENGVAXIA on milk production, its presence in breast milk, or its effects on the breastfed child. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DENGVAXIA and any potential adverse effects on the breastfed child from DENGVAXIA or from the underlying maternal condition. For preventive vaccines, the underlying condition is susceptibility to disease prevented by the vaccine. A lactation study in which female mice were administered a single dose of DENGVAXIA on day 14 of lactation did not show the presence of DENGVAXIA in breast milk.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Vertical transmission of dengue virus, including potentially through breastmilk, has been reported.

Fetal/neonatal adverse reactions

Vaccine viremia can occur 7 to 14 days after vaccination with a duration of <7 days. *[See Pharmacokinetics (12.3).]* The potential for transmission of the vaccine virus from mother to infant through breastmilk is unknown.

Animal Data

A developmental toxicity study in which female mice were administered a single injection of 5 log_{10} $CCID_{50}$ (full human dose ranging from 4.5 log_{10} to 6.0 log_{10} $CCID_{50}$), 6.5 log_{10} $CCID_{50}$ or 8 log_{10} $CCID_{50}$ of DENGVAXIA by intravenous injection on Day 14 of lactation did not show the presence of DENGVAXIA in breast milk in mice when measured 24 hours after vaccine administration.

8.4 Pediatric Use

Safety and effectiveness of DENGVAXIA in children younger than 9 years of age have not been established.

8.5 Geriatric Use

Safety and effectiveness of DENGVAXIA in adults 65 years of age and older have not been established.

11 DESCRIPTION

DENGVAXIA (Dengue Tetravalent Vaccine, Live) is a sterile suspension for subcutaneous injection. DENGVAXIA is supplied as a vial of lyophilized vaccine antigen, which must be reconstituted at the time of use with 0.6 mL from the accompanying vial of diluent (0.4% sodium chloride). After reconstitution, DENGVAXIA is a clear, colorless suspension (trace amounts of white to translucent proteinaceous particles may be present). *[See Dosage and Administration (2.3).]*

After reconstitution, each 0.5 mL dose of DENGVAXIA contains 4.5 - 6.0 $\log_{10}$ $CCID_{50}$ of each of the chimeric yellow fever dengue (CYD) virus serotypes 1, 2, 3, and 4. Each 0.5 mL dose is formulated to contain 2 mg sodium chloride and the following ingredients as stabilizers: 0.56 mg essential amino acids (including L-phenylalanine), 0.2 mg non-essential amino acids, 2.5 mg L-arginine hydrochloride, 18.75 mg sucrose, 13.75 mg D-trehalose dihydrate, 9.38 mg D-sorbitol, 0.18 mg trometamol, and 0.63 mg urea.

Each of the four CYD viruses (CYD-1, CYD-2, CYD-3, and CYD-4) in DENGVAXIA was constructed using recombinant DNA technology by replacing the sequences encoding the pre-membrane (prM) and envelope (E) proteins in the yellow fever (YF) 17D204 vaccine virus genome with those encoding for the homologous sequences of dengue virus serotypes 1, 2, 3, and 4, respectively. Each CYD virus is cultured separately in Vero cells (African Green Monkey kidney) under serum-free conditions, harvested from the supernatant of the Vero cells and purified by membrane chromatography and ultrafiltration. The purified and concentrated harvest of each CYD virus is then diluted in a stabilizer solution to produce the four monovalent drug substances. The final bulk product is a mixture of the four monovalent drug substances diluted in the stabilizer solution. The final bulk product is sterilized by filtration at 0.22 µm, filled into vials and freeze-dried.

DENGVAXIA does not contain preservative.

The vial stoppers for the Lyophilized Vaccine Antigen and Diluent vials of DENGVAXIA are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Following administration, DENGVAXIA elicits dengue-specific immune responses against the four dengue virus serotypes. The exact mechanism of protection has not been determined.

12.3 Pharmacokinetics

Viremia

In studies that evaluated the occurrence of vaccine viremia systematically at pre-specified time-points, vaccine viremia (measured by genomic amplification methods) was observed following vaccination with DENGVAXIA in 5.6% of subjects, with 90% of these occurrences documented after the first injection. Vaccine viremia was observed 7 to 14 days after DENGVAXIA vaccination with a duration of <7 days.

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

DENGVAXIA has not been evaluated for carcinogenic or mutagenic potential or impairment of male fertility. Exposure of female rabbits to DENGVAXIA prior to and during gestation did not impair fertility. *[See Use in Specific Populations (8.1).]*

14 CLINICAL STUDIES

14.1 Efficacy

The efficacy of DENGVAXIA was evaluated in two randomized, observer-blind, placebo-controlled, multi-center studies. Study 1 (N=20,869) was conducted in individuals 9 through 16 years of age in four Latin American countries and Puerto Rico; and Study 2 (N=10,275) was conducted in individuals 2 through 14 years of age in five Asia-Pacific countries. A subset of subjects in each study (10% in Study 1; 20% in Study 2) was evaluated for antibodies to dengue virus at the time of enrollment and at later time points. Both studies enrolled subjects irrespective of evidence of previous dengue infection. Subjects were randomized 2:1 to receive either DENGVAXIA or saline placebo and were monitored for symptomatic virologically-confirmed dengue (VCD) starting at Day 0. Per protocol vaccine efficacy was assessed beginning 28 days after the third vaccination for 12 months. VCD was defined as an acute febrile illness (temperature ≥38°C on at least 2 consecutive days) virologically-confirmed by dengue RT-PCR and/or dengue non-structural protein 1 (NS1) ELISA Antigen Test. For each study, in pre-specified vaccine efficacy analyses including the full age range of subjects enrolled, the pre-specified criterion for demonstrating efficacy of DENGVAXIA against VCD due to any dengue virus serotype and irrespective of previous dengue virus infection, was met (lower bound of 95% CI for vaccine efficacy >25%). These studies were not designed to demonstrate efficacy of DENGVAXIA against individual dengue serotypes.

Given the identification of the increased risk for severe dengue following vaccination with DENGVAXIA and subsequent infection with dengue virus in persons not previously infected with dengue virus *[see Adverse Reactions (6.1)]*, Table 3 presents analyses of vaccine efficacy against VCD due to any dengue virus serotype, limited to subjects who had baseline sera evaluated and who were dengue seropositive at baseline. These analyses include subjects 9 through 16 years of age from Study 1 and subjects 9 through 14 years of age from Study 2.

Table 3: Efficacy of DENGVAXIA against Symptomatic VCD in Subjects Seropositive for Dengue at Baseline from 28 Days Post-Dose 3 for a Period of 12 months – Study 1 (Ages 9 through 16 Years) and Study 2 (Ages 9 through 14 Years) – mFASE* – Subjects Included in the Immunogenicity Subset

	DENGVAXIA group Cases (Subjects)	Placebo group Cases (Subjects)	VE % (95% CI)†
Study 1 (Subjects 9 through 16 years of age)	7 (1034)	17 (492)	80.6 (50.7;93.2)
Study 2 (Subjects 9 through 14 years of age)	4 (483)	9 (250)	77.2 (18.3;94.9)

* mFASE (Modified Full Analysis Set): Set of the subjects who received 3 injections as per randomization including those with protocol deviations.

† VE is calculated as 1- ratio of density incidence of dengue between DENGVAXIA and Placebo groups.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

An outer package of 1 dose (NDC 49281-605-01) contains 1 single dose vial of Lyophilized Vaccine Antigen (NDC 49281-606-58) and 1 single dose vial of Saline Diluent (NDC 49281-546-68).

The vial stoppers for the Lyophilized Vaccine Antigen vials and the Saline Diluent vials of DENGVAXIA are not made with natural rubber latex.

16.2 Storage and Handling

Store Lyophilized Vaccine Antigen and Saline Diluent in a refrigerator at 2°C to 8°C (36°F to 46°F). **Do not freeze**. Protect from light.

Do not use after the expiration date shown on the vial labels of the Lyophilized Vaccine Antigen and Saline Diluent.

After reconstitution, administer DENGVAXIA immediately or store refrigerated at 2°C to 8°C (36°F to 46°F) and use within 30 minutes. Discard reconstituted vaccine if not used within 30 minutes.

17 PATIENT COUNSELING INFORMATION

Educate vaccine recipients regarding the most common adverse reactions that occur within 14 days following administration of DENGVAXIA (headache, injection site pain, malaise, asthenia, and myalgia).

Inform individuals to seek medical care if they develop signs and symptoms of dengue fever with particular attention to severe dengue warning signs (e.g., high fever, severe abdominal pain or tenderness, persistent vomiting, mucosal bleeding, somnolence and hyperactivity).

Register women who receive DENGVAXIA during pregnancy in the Pregnancy Registry by calling 1-800-822- 2463 (1-800-VACCINE). *[See Pregnancy (8.1).]*

Instruct vaccine recipients to report adverse reactions to their healthcare provider.

Manufactured and distributed by:
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