Summary of Product Characteristics
QDENGA®
Dengue Tetravalent Vaccine (Live, Attenuated)

1. Name of the Medicinal Product

QDENGA® (DENGUE TETRAVALENT VACCINE (LIVE, ATTENUATED))

2. Qualitative and Quantitative Composition

After reconstitution, 1 dose (0.5 mL) contains:

Live attenuated dengue virus serotype 1*: ≥ 3.3 log10 PFU**/dose

Live attenuated dengue virus serotype 2#: ≥ 3.1 log10 PFU**/dose

Live attenuated dengue virus serotype 3*: ≥ 4.0 log10 PFU**/dose

Live attenuated dengue virus serotype 4*: ≥ 4.5 log10 PFU**/dose

*Produced in Vero cells by recombinant DNA technology. Genes of serotype-specific surface proteins engineered into dengue type 2 backbone

#Produced in Vero cells by recombinant DNA technology

**PFU = Plaque-forming units

For excipients, see section 6.1.

3. Pharmaceutical Form

Powder and diluent (solvent) for solution for injection.

Prior to reconstitution, the vaccine is a white to off-white colored freeze-dried powder (compact cake).

The diluent (solvent) is a clear, colorless solution.

4. Clinical Particulars

4.1 Therapeutic Indications

Qdenga® is indicated for the prevention of dengue disease caused by any dengue virus serotype in individuals 6 years to 45 years of age.

The use of Qdenga® should be in accordance with official recommendations.

4.2 Posology and Method of Administration

Dosage

Individuals 6 to 45 years of age at time of first injection
Qdenga® should be administered as a 0.5 mL dose at a two-dose (0 and 3 months) schedule.

The need for a booster dose has not been established.

Special Patient Populations

Impaired Renal Function

The safety and efficacy of Qdenga® in this population not been established.

Impaired Hepatic Function

The safety and efficacy of Qdenga® in this population not been established.

Elderly Patients

Qdenga is not indicated in individuals above 45 years of age.

Pediatric patients

Qdenga is not indicated in children below 6 years of age.

Method of administration

After complete reconstitution of the lyophilized vaccine with the diluent (solvent), Qdenga® should be administered by subcutaneous (SC) injection preferably in the upper arm in the region of deltoid.

Qdenga® must not be injected intravascularly, intradermally or intramuscularly. The vaccine should not be mixed in the same syringe with any vaccines or other parenteral medicinal products.

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

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1. or hypersensitivity to a previous dose of Qdenga®.
- Individuals with congenital or acquired immune deficiency, including immunosuppressive therapies such as chemotherapy or high doses of systemic corticosteroids (e.g., 20 mg/day or 2 mg/kg/day of prednisone for 2 weeks or more) within 4 weeks prior to vaccination, as with other live attenuated vaccines
- Individuals with symptomatic HIV infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function.
- Pregnant women (see section 4.6 “Pregnancy and Lactation”)
- Breast-feeding women (see section 4.6 “Pregnancy and Lactation”)

4.4 Special Warnings and Special Precautions for Use

Anaphylaxis

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in the event of a rare anaphylactic reaction following administration of the vaccine.

Review of medical history
Vaccination should be preceeded by a review of the medical history (especially with regard to previous vaccination and possible hypersensitivity reactions which occurred after vaccination).

Concurrent illness
Vaccination with Qdenga® should be postponed in subjects suffering from an acute severe febrile illness. The presence of a minor infection, such as a cold, should not result in a deferral of vaccination.

Limitations of vaccine effectiveness
A protective immune response with Qdenga® may not be elicited in all vaccinees against all serotypes of dengue virus and may decline over time (see section 5.1 "Pharmacodynamic properties"). It is currently unknown whether a lack of protection could result in an increased severity of dengue. It is recommended to continue personal protection measures against mosquito bites after vaccination. Individuals should seek medical care if they develop dengue symptoms or dengue warning signs.

Anxiety related reactions
Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress - related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

Women of childbearing potential
As with other live attenuated vaccines, women of childbearing potential should avoid pregnancy for at least one month following vaccination (see section 4.6 "Pregnancy and Lactation").

Other
Qdenga® must not be administered by intravascular, intradermal or intramuscular injection.

4.5 Interaction with Other Medications and Other Forms of 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 Qdenga®, to avoid neutralization of the attenuated viruses contained in the vaccine.

Qdenga® 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 "Contraindications").

Use with other vaccines
If Qdenga® is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

Qdenga® may be administered concomitantly with a hepatitis A vaccine. Coadministration has

been studied in adults.

Qdenga® may be administered concomitantly with a yellow fever vaccine. Coadministration has been studied in adults. In a clinical study involving approximately 300 subjects who received Qdenga® concomitantly with yellow fever 17D vaccine, there was no effect on the yellow fever seroprotection rates. Dengue antibody responses were decreased following concomitant administration of Qdenga® and yellow fever 17D vaccine. The clinical significance of this finding is unknown.

4.6 Pregnancy and Lactation

Women of childbearing potential
Women of childbearing potential should avoid pregnancy for at least one month following vaccination. Women who intend to become pregnant should be advised to delay.

Pregnancy
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3 “Nonclinical safety data”).

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

Qdenga® is a live attenuated vaccine, therefore Qdenga® is contraindicated during pregnancy (see section 4.3 “Contraindications”).

Breast-feeding
It is unknown whether Qdenga® is excreted in human milk. A risk to the newborns/infants cannot be excluded.
Qdenga® is contraindicated during breast-feeding (see section 4.3 “Contraindications”).

Fertility
Animal studies did not indicate any harmful effects with respect to female fertility (see section 5.3 “Nonclinical safety data”). No specific studies have been performed on fertility in humans.

4.7 Effects on ability to drive and use machines

No studies on the effects of Qdenga® on the ability to drive and use machines have been performed. Some of the effects mentioned under section 4.8 “Undesirable effects” may temporarily have a minor influence on the ability to drive and use machines.

4.8 Undesirable effects

Clinical Studies
In clinical studies, the most frequently reported reactions in subjects aged 6 to 45 years of age were injection site pain (54%), headache (36%), myalgia (34%), injection site erythema (29%), malaise (24%), asthenia (21%) and fever (10%).

These adverse reactions usually occurred within 2 days after the injection, were mild to moderate in severity, had a short duration (1 to 3 days) and were less frequent after the second injection of Qdenga® than after the first injection.

Vaccine viremia
In clinical study DEN-205, transient vaccine viremia was observed after vaccination with Qdenga® in 49% of study participants who had not been infected with dengue before and in 16% of study participants who had been infected with dengue before. Vaccine viremia usually started in the second week after the first injection and had a mean duration of 4 days. Vaccine viremia was associated with transient, mild to moderate symptoms, such as headache, arthralgia, myalgia and rash in some subjects.

Tabulated list of adverse reactions
Adverse reactions associated with Qdenga® obtained from clinical studies are tabulated below.

The safety profile presented below is based on a pooled analysis including 12544 study participants aged 6 to 45 years (12098 children and 446 adults) who have been vaccinated with Qdenga®. This included a reactogenicity subset of 3131 participants (2685 children and 446 adults).

Adverse reactions are listed according to the following frequency categories:

Very common: ≥1/10
Common: ≥1/100 to <1/10
Uncommon: ≥1/1,000 to <1/100
Rare: ≥1/10,000 to <1/1,000
Very rare: <1/10,000

Table 1: Adverse reactions from Clinical Studies (Age 6 to 45 years)

System Organ Class	Frequency	Adverse Reactions
Infections and infestations	Very common	Upper respiratory tract infection [a]
	Common	Nasopharyngitis Pharyngotonsillitis [b]
	Uncommon	Bronchitis Rhinitis
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness

System Organ Class	Frequency	Adverse Reactions
Gastrointestinal disorders	Uncommon	Diarrhoea Nausea Abdominal pain Vomiting
Skin and subcutaneous tissue disorders	Uncommon	Rash [c] Pruritus [d] Urticaria
	Very rare	Angioedema
Musculoskeletal and connective tissue disorders	Very common	Myalgia
	Common	Arthralgia
General disorders and administration site conditions	Very common	Injection site pain Injection site erythema Malaise Asthenia Fever
	Common	Injection site swelling Injection site bruising [d] Injection site pruritus [d] Influenza like illness
	Uncommon	Injection site haemorrhage [d]

Adverse reactions included as preferred term are based on MedDRA version 23.0
[a] Includes upper respiratory tract infection and viral upper respiratory tract infection
[b] Includes pharyngotonsillitis and tonsillitis
[c] Includes rash, viral rash, rash maculopapular, rash pruritic
[d] Reported in adults aged up to 45 years in clinical trials
Two additional adverse reactions with uncommon frequency (fatigue and injection site discolouration) were reported in subjects aged 46 years and older and are provided for information as those events are considered representative of adults of any age.

Paediatric population

Paediatric data in subjects 6 to 17 years of age

Pooled safety data from clinical trials are available for 12098 children. This includes reactogenicity data collected in 2685 children.

Frequency, type and severity of adverse reactions in children were largely consistent with those in adults. Adverse reactions reported more commonly in children than in adults were fever (10% versus 3%), upper respiratory tract infection (11% versus 3%), nasopharyngitis (6% versus 0.7%), pharyngotonsillitis (2% versus 0.5%), and influenza like illness (1% versus 0.2%). Adverse reactions reported less commonly in children than adults were injection site erythema (2% versus 29%), nausea (0.04% versus 0.7%) and arthralgia (0.04% versus 1%).

Paediatric data in subjects below 6 years of age, i.e. outside the age indication
Reactogenicity was assessed in 370 subjects below 6 years of age. Reactions reported with very common frequency were injection site pain (30%), decreased appetite (17%), fever (14%), irritability (13%), somnolence (13%), headache (10%), malaise (10%), and myalgia (10%). Asthenia (8%), nasopharyngitis (6%), injection site swelling (3%), urticaria (1%), and injection site erythema (1%) were reported with common frequency.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of Qdenga ® is important. It allows continued monitoring of the benefit/risk balance of Qdenga ®. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system (e-meso.pom.go.id) and/or to Takeda Indonesia (email: AE.Indonesia@takeda.com).

4.9 Overdose
No cases of overdose have been reported.

4.10 Drug Abuse and Dependence
Qdenga® has no known potential for abuse or dependence.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

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

Clinical Studies

1. Mechanism of action

Qdenga® contains live attenuated dengue viruses.
The primary mechanism of action of Qdenga® is to replicate locally and elicit neutralizing antibodies to confer protection against dengue disease caused by any of the four dengue virus serotypes. Qdenga® activates multiple arms of the immune system, including binding antibodies, complement fixing antibodies, functional antibodies to dengue nonstructural protein 1 (NS1), and cell mediated immune responses (CD4+, CD8+, and natural killer cells).

2. Clinical efficacy

The clinical efficacy of Qdenga® was assessed in study DEN-301, a pivotal Phase 3, double-blind, randomized, placebo-controlled study conducted across 5 countries in Latin America (Brazil, Colombia, Dominican Republic, Nicaragua, Panama) and 3 countries in Asia (Sri Lanka, Thailand, the Philippines). A total of 20,099 children aged between 4 and 16 years were randomized (2:1 ratio) to receive Qdenga® or placebo, regardless of previous dengue infection.

The dengue serostatus at baseline (before the first injection) was assessed in all subjects by Micro Neutralization Test (MNT50) to allow Vaccine Efficacy (VE) assessment by baseline serostatus. The baseline dengue seronegativity rate for the overall per protocol population was 27.7%.

Efficacy was assessed using active surveillance across the entire study duration. Any subject with febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) was required to visit the

study site for dengue fever evaluation by the investigator. Subjects/guardians were reminded of this requirement at least weekly to maximize the detection of all symptomatic virologically-confirmed dengue (VCD). Febrile episodes were confirmed by a validated, quantitative dengue RT-PCR to detect specific dengue serotypes.

2.1 Clinical efficacy data from DEN-301 study (subjects 4 to 16 years of age)

The Vaccine Efficacy (VE) results, according to the primary endpoint (VCD fever occurring from 30 days to 12 months after the second vaccination) are shown in **Table 2**.

Table 2: Vaccine Efficacy in Preventing VCD Fever Caused by any Serotype From 30 Days to 12 Months Post Second Vaccination in Study DEN-301 (Per Protocol Set)

	Qdenga®	**Placebo**
	N = 12,700[a]	**N = 6316[a]**
VCD fever, n (%)	61 (0.5)	149 (2.4)
Vaccine efficacy (95% CI) (%)	80.2 (73.3, 85.3)	
p-value	<0.001	

CI: confidence interval; n: number of subjects with fever; VCD: virologically confirmed dengue.
[a] Number of subjects evaluated

VE results according to the secondary endpoints, preventing hospitalization due to VCD fever, preventing VCD fever by serostatus, by serotype and preventing severe VCD fever are shown in **Table 3**. For severe VCD fever, two types of endpoints were considered: clinically severe VCD cases and VCD cases that met the 1997 WHO criteria for Dengue Haemorrhagic Fever (DHF).

Table 3: Vaccine Efficacy in Preventing Hospitalization due to VCD Fever, in Preventing VCD Fever by Dengue Serotype, in Preventing VCD Fever by Baseline Dengue Serostatus, and in Preventing Severe Forms of Dengue from 30 Days to 18 Months Post Second Vaccination in study DEN-301 (Per Protocol Set)

	Qdenga® N=12,700[a]	**Placebo** N=6316[a]	**VE (95% CI)**
VE in preventing hospitalizations due to VCD fever[b], n (%)			
Hospitalizations due to VCD fever	13 (0.1)	66 (1.0)	90.4 (82.6, 94.7)[c]
VE in preventing VCD fever by dengue serotype, n (%)			
VCD fever caused by DENV-1	38 (0.3)	62 (1.0)	69.8 (54.8, 79.9)
VCD fever caused by DENV-2	8 (<0.1)	80 (1.3)	95.1 (89.9, 97.6)
VCD fever caused by DENV-3	63 (0.5)	60 (0.9)	48.9 (27.2, 64.1)
VCD fever caused by DENV-4	5 (<0.1)	5 (<0.1)	51.0 (-69.4, 85.8)
VE in preventing VCD fever by baseline dengue serostatus, n (%)			
VCD fever in all subjects	114 (0.9)	206 (3.3)	73.3 (66.5, 78.8)
VCD fever in baseline seropositive	75 (0.8)	150 (3.3)	76.1 (68.5, 81.9)
VCD fever in baseline seronegative	39 (1.1)	56 (3.2)	66.2 (49.1, 77.5)
VE in preventing DHF induced by any dengue serotype, n (%)			
Overall	2 (<0.1)	7 (0.1)	85.9 (31.9, 97.1)
VE in preventing severe dengue induced by any dengue serotype, n (%)			
Overall	2 (<0.1)	1 (<0.1)	2.3 (-977.5, 91.1)

CI: confidence interval; n: number of subjects; VCD: virologically confirmed dengue; DENV: dengue virus serotype.
[a] Number of subjects evaluated.
[b] key secondary endpoint.
[c] p-value<0.001.

Rapid onset of protection was seen with an exploratory VE of 81.1% (95% CI: 64.1%, 90.0%) against VCD fever caused by all serotypes combined from first vaccination until second vaccination.

2.2 Clinical Efficacy for subjects 17 to 60 years of age

No clinical efficacy study has been conducted in subjects from 17 to 60 years of age. The clinical efficacy of Qdenga® is based on bridging of immunogenicity data (see subsection 3.2 below).

2.3 Long term protection

In study DEN-301, a number of exploratory analyses were conducted to estimate long term protection from first dose to 3 years after the second dose (**Table 4)**.

Table 4: Vaccine Efficacy in Preventing VCD Fever and Hospitalization overall and by Baseline Dengue Serostatus from first dose to 3 Years Post Second Dose in Study DEN-301 (Safety Set)

	VE (95% CI) in preventing VCD Fever N = 20,067	VE (95% CI) in preventing Hospitalization due to VCD Fever N = 20,067
Overall	62.0 (56.6, 66.7)	83.6 (76.8, 88.4)
By baseline dengue serostatus		
Seropositive	65.0 (58.9, 70.1)	86.0 (78.4, 91.0)
Seronegative	54.3 (41.9, 64.1)	77.1 (58.6, 87.3)

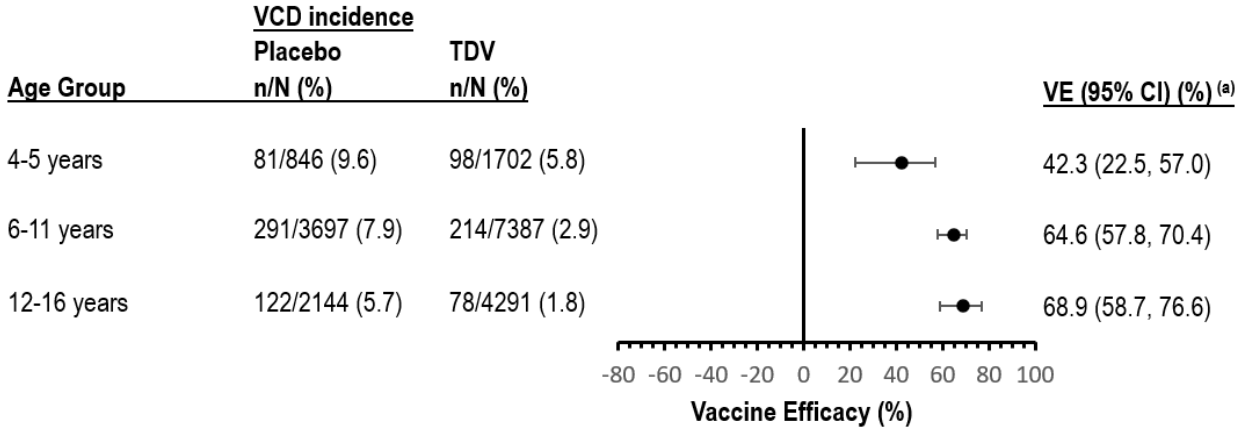
VE: vaccine efficacy, CI: confidence interval, VCD: virologically confirmed dengue, N: total number of subjects

Additionally, VE in preventing DHF caused by any serotype was 65.4% (95% CI: 19.0%, 85.2%) and in preventing clinically severe VCD cases caused by any serotype was 70.2% (95% CI: -24.7%, 92.9%).

Up to three years after the second dose, VE in preventing VCD was shown for all four serotypes in baseline dengue seropositive subjects. In baseline seronegative subjects, VE was shown for DENV-1 and DENV-2, but not suggested for DENV-3 and could not be shown for DENV-4 due to lower incidence of cases.

Figure 1 shows the effect of Qdenga in different age groups in Trial DEN-301.

Figure 1: Trial DEN-301: Forest Plot of Vaccine Efficacy (95% Confidence Interval) for VCD (Overall) From First Dose to 36 Months Post Second Vaccine Dose by Age Group (Safety Set)



Abbreviations: CI, confidence interval; n, number of subjects with VCD fever; N, total number of evaluable subjects; NE, not estimable; VCD, virologically confirmed dengue; VE, vaccine efficacy.

(a) VE was defined as 1 - (λ_V/λ_C), where λ_V and λ_C denote the hazard rates for developing VCD fever for the TDV and placebo arms, respectively.

3. Immunogenicity

During clinical development, immunogenicity data were collected in 7 studies with 3717 subjects who received 2 doses of Qdenga® 3 months apart; 2796 of these subjects lived in dengue endemic areas and 921 subjects lived in non-endemic areas.

Neutralizing antibody titers for each serotype were measured with the microneutralization test (MNT_{50}) and presented as Geometric Mean Titers (GMTs).
In the tables below the dengue serostatus at baseline (before the first injection) was identified as:

- Dengue seropositive if the MNT_{50} titer was ≥10 (the lower limit of detection, LLOD), against at least one serotype.
- Dengue seronegative if the MNT_{50} titer was < the LLOD against all 4 serotypes.

3.1 Immunogenicity data from DEN-301 study (subjects 4 to 16 years of age)

The GMTs by baseline dengue serostatus in subjects 4 to 16 years of age in study DEN-301 are shown in **Table 5**.

Table 5: Immunogenicity by Baseline Dengue Serostatus in Study DEN-301 (Per Protocol Set for Immunogenicity)

	Baseline Seropositive		**Baseline Seronegative**	
	Pre-Vaccination N=1816*	1 month Post-Dose 2 N=1621	Pre-Vaccination N=702	1 month Post-Dose 2 N=641
DENV-1				
GMT	411.3	2115.2	5.0	184.2
95% CI	(366.0, 462.2)	(1957.0, 2286.3)	NE**	(168.6, 201.3)
DENV-2				
GMT	753.1	4897.4	5.0	1729.9
95% CI	(681.0, 832.8)	(4645.8, 5162.5)	NE**	(1613.7, 1854.6)
DENV-3				
GMT	357.7	1761.0	5.0	228.0
95% CI	(321.3, 398.3)	(1645.9, 1884.1)	NE**	(211.6, 245.7)
DENV-4				
GMT	218.4	1129.4	5.0	143.9
95% CI	(198.1, 240.8)	(1066.3, 1196.2)	NE**	(133.6, 155.1)

N: number of subjects evaluated; DENV: Dengue virus; GMT: Geometric Mean Titer; CI: confidence interval; NE: not estimated
* For DENV-2 and DENV-3 N= 1815
** All subjects had GMT values below LLOD (10), hence were reported as 5 with no CI values

3.2 Immunogenicity data from DEN-304 study (subjects 18 to 60 years of age)

The immunogenicity of Qdenga® in adults 18 to 60 years of age was assessed in DEN-304, a Phase 3 double-blind, randomized, placebo-controlled study in a non-endemic country (US). The post-dose 2 GMTs are shown in **Table 6a and Table 6b**.

Table 6a: GMTs of Dengue Neutralizing Antibodies in Baseline Seronegative Subjects in Study DEN-304 (Per Protocol Set)

	Age 18-30		Age 31-45		Age 46-60	
	Pre-Vaccination N=94	1 month Post-Dose 2 N=91	Pre-Vaccination N=125	1 month Post-Dose 2 N=119	Pre-Vaccination N=160	1 month Post-Dose 2 N=157
DENV-1 GMT 95% CI	5.0 NE**	251.1 (190.8, 330.6)	5.0 NE**	245.7 (181.1, 333.3)	5.0 NE**	297.6 (223.9, 395.5)
DENV-2 GMT 95% CI	5.0 NE**	2575.6 (2008.1, 3303.4)	5.0 NE**	3298.3 (2743.6, 3965.3)	5.0 NE**	2948.5 (2460.6, 3533.2)
DENV-3 GMT 95% CI	5.0 NE**	106.9 (84.5, 135.3)	5.0 NE**	131.6 (101.2, 171.1)	5.0 NE**	141.3 (114.2, 175.0)
DENV-4 GMT 95% CI	5.0 NE**	123.0 (101.4, 149.3)	5.0 NE**	141.9 (111.5, 180.5)	5.0 NE**	143.1 (118.9, 172.2)

N: number of subjects evaluated; DENV: Dengue virus; GMT: Geometric Mean Titer; CI: confidence interval; NE: not estimated
Pooled data from Dengue tetravalent vaccine Lots 1, 2 and 3
** All subjects had GMT values below LLOD (10), hence were reported as 5 with no CI values

Table 6b: GMTs of Dengue Neutralizing Antibodies in Baseline Seropositive Subjects in Study DEN-304 (Per Protocol Set)

	Age 18-30		Age 31-45		Age 46-60	
	Pre-Vaccination N=15	1 month Post-Dose 2 N=14	Pre-Vaccination N=28	1 month Post-Dose 2 N=28	Pre-Vaccination N=25	1 month Post-Dose 2 N=25
DENV-1 GMT 95% CI	13.6 (6.2, 30.0)	333.3 (104.3, 1065.2)	9.6 (5.9, 15.5)	288.5 (155.8, 534.4)	21.4 (9.8, 47.2)	500.2 (216.5, 1155.5)
DENV-2 GMT 95% CI	35.0 (16.5, 74.4)	2786.7 (996.7, 7791.3)	27.5 (18.6, 40.5)	3674.6 (2361.4, 5717.9)	35.3 (16.5, 75.5)	2715.2 (1582.8, 4658.0)
DENV-3 GMT 95% CI	7.1 (4.2, 12.1)	171.5 (71.0, 414.1)	5.7 (4.7, 7.0)	162.8 (81.4, 325.4)	10.0 (5.4, 18.5)	224.9 (143.0, 353.6)
DENV-4 GMT 95% CI	7.1 (4.2, 12.1)	187.8 (59.8, 589.8)	5.0 NE**	196.8 (104.4, 371.1)	11.5 (5.5, 24.1)	305.2 (147.6, 631.0)

N: number of subjects evaluated; DENV: Dengue virus; GMT: Geometric Mean Titer; CI: confidence interval; NE: not estimated
Pooled data from Dengue tetravalent vaccine Lots 1, 2 and 3
** All subjects had GMT values below LLOD (10), hence were reported as 5 with no CI values

The bridging of efficacy is based on immunogenicity data and results from a non-inferiority analysis, comparing post-vaccination GMTs in the baseline dengue seronegative populations of DEN-301 and DEN-304 **(Table 7)**. Protection against dengue disease is expected in adults

although the actual magnitude of efficacy relative to that observed in children and adolescents is unknown.

Table 7: GMT Ratios between Baseline Dengue Seronegative subjects in DEN-301 (4-16 years) and DEN-304 (18-60 years)

GMT Ratio* (95% CI)	DENV-1	DENV-2	DENV-3	DENV-4
1m post-2nd dose	0.69 (0.58, 0.82)	0.59 (0.52, 0.66)	1.77 (1.53, 2.04)	1.05 (0.92, 1.20)
6m post-2nd dose	0.62 (0.51, 0.76)	0.66 (0.57, 0.76)	0.98 (0.84, 1.14)	1.01 (0.86, 1.18)

DENV: Dengue virus; GMT: Geometric Mean Titer; CI: confidence interval; m: month(s)
*Non-inferiority: upper bound of the 95% CI less than 2.0.

3.3 Long-term persistence of antibodies

The long-term persistence of neutralizing antibodies was shown in study DEN-204, a Phase 2 study in subjects 2-17 years of age in endemic countries, with titers remaining well above the pre-vaccination levels for all four serotypes, up to 48 months after the first dose.

5.2 Pharmacokinetic Properties

No pharmacokinetic studies have been performed with Qdenga®.

5.3 Nonclinical Safety Data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal Toxicology and/or Pharmacology

Non-clinical safety data revealed no special hazard for humans based on conventional studies of single dose, local tolerance, repeated dose toxicity, and toxicity to reproduction and development.

In a distribution and shedding study, there was no shedding of Qdenga® RNA in feces and urine, confirming a low risk for vaccine shedding to the environment or transmission from vaccinees. A neurovirulence study shows that Qdenga® is not neurotoxic.

6. Pharmaceutical Particulars

6.1 List of Excipients

Powder:
α,α-Trehalose dihydrate
Poloxamer 407
Human serum albumin
Potassium dihydrogen phosphate
Disodium hydrogen phosphate
Potassium chloride
Sodium chloride

Diluent (Solvent):
Sodium chloride
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other vaccine or medicinal products except for the diluent (solvent) provided.

6.3 Stability after reconstitution

After reconstitution with the diluent (solvent) provided:
Qdenga® should be used immediately.
If not used immediately Qdenga® must be used within 2 hours.

6.4 Special Precautions for Storage

Store at a temperature between +2 °C and +8 °C. Do not freeze.
Store in the original package.

6.5 Nature and Contents of Container

Qdenga® powder and diluent (solvent) for solution for injection:

- Powder (1 dose) in glass vial (Type-I glass), with a stopper (butyl rubber) and aluminum seal with green flip-off plastic cap + diluent (solvent) in glass vial (Type-I glass), with a stopper (bromobutyl rubber) and aluminum seal with purple flip-off plastic cap
    - Pack size of 1 : DKIXXXXXXXXXXX
    - Pack size of 10 : DKIXXXXXXXXXXX

Qdenga® powder and diluent (solvent) for solution for injection in pre-filled syringe:

- Powder (1 dose) in vial (Type-I glass), with a stopper (butyl rubber) and aluminum seal with green flip-off plastic cap + diluent (solvent) in pre-filled syringe (Type-I glass), with a plunger stopper (bromobutyl) and a tip cap (polypropylene), with 2 separate needles
    - Pack size of 1 : DKIXXXXXXXXXXX
    - Pack size of 5 : DKIXXXXXXXXXXX

Not all pack sizes may be marketed.

6.6 Instructions for Use/Handling

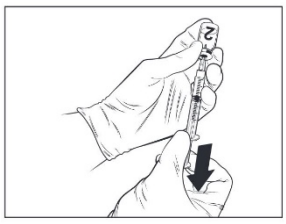
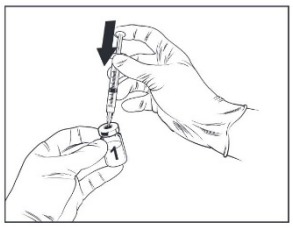
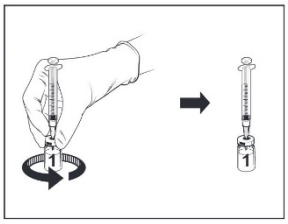
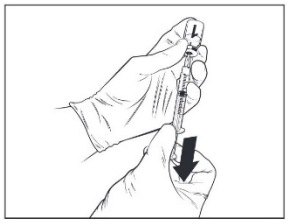
Contact with preservatives, antiseptics, detergents, and other anti-viral substances is to be avoided since they may inactivate the vaccine. Use only sterile syringes that are free of preservatives, antiseptics, detergents, and other anti-viral substances for reconstitution and injection of Qdenga®.

Qdenga® must be reconstituted prior to administration.

Use only the diluent (solvent) (0.22% sodium chloride solution) supplied with the vaccine since it is free of preservatives or other anti-viral substances.

Instructions for reconstitution of the vaccine with the diluent (solvent) presented in vial

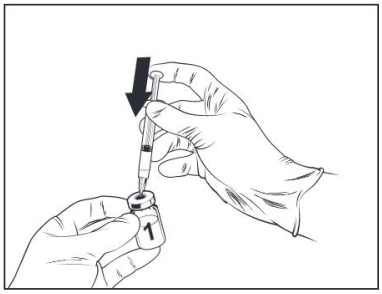
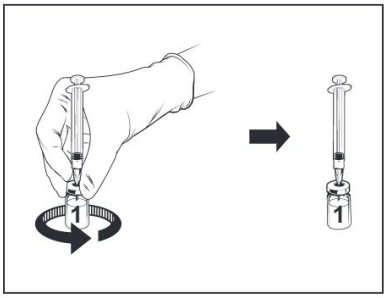
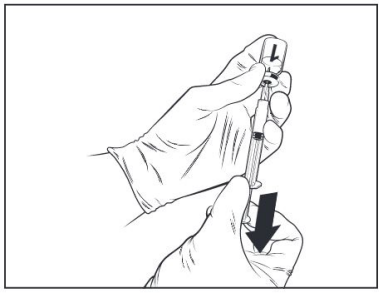
Qdenga® is a 2-component vaccine that consists of a vial containing lyophilized vaccine and a vial containing diluent. The lyophilized vaccine must be reconstituted with diluent prior to administration. Remove the vaccine and diluent vials from the refrigerator and place at room temperature for approximately 15 minutes. Remove the caps from both vials and clean the surface of stoppers on top of the vials using an alcohol wipe. Using a graduated syringe, withdraw the entire contents of the diluent vial and slowly inject into the lyophilized vaccine vial. Making sure to keep the vial upright, slowly swirl with syringe still inserted into vial until the vaccine is completely dissolved. Withdraw the entire volume of the reconstituted vaccine with the same syringe and needle. Following reconstitution, the resulting solution should be clear, colorless to pale yellow, and essentially free of foreign particulates. Discard the attached needle and replace with a new 25-gauge 5/8" needle prior to administration.

 Diluent Vial	 Lyophilised Vaccine Vial	 Reconstituted Vaccine	 Reconstituted Vaccine
1. Attach a 23-gauge 1" needle to a 1 mL syringe and insert the needle into the diluent vial. Slowly press the plunger completely down. Turn the vial upside down, withdraw the entire contents of the vial and continue to pull plunger out to 0.75 mL. A bubble should be seen inside of the syringe. Invert the syringe to bring the bubble back to the plunger.	2. Insert the needle of the syringe assembly into the lyophilized vaccine vial and direct the flow of the diluent toward the side of the vial while slowly depressing the plunger to reduce the chance of forming bubbles.	3. Release your finger from the plunger and, holding the assembly on a flat surface, gently swirl the vial in both directions with the needle syringe assembly attached. DO NOT SHAKE. Foam and bubbles may form in the reconstituted product if it is shaken. Let the vial and syringe assembly sit for a while until the solution becomes clear. This takes about 30-60 seconds.	4. Withdraw the entire volume of the reconstituted Qdenga® solution until an air bubble appears in the syringe. Remove the needle syringe assembly from the vial. Hold the syringe with the needle pointing upwards, tap the side of the syringe to bring the air bubble to the top, discard the attached needle and replace with a new 25-gauge 5/8" needle, expel the air bubble until a small drop of the liquid forms at the top of the needle. Qdenga® is ready to be administered by subcutaneous injection.

After reconstitution Qdenga® should be administered immediately. If not used immediately Qdenga® must be used within 2 hours. The reconstituted vaccine can remain in the vial or in the syringe for this period without loss in potency.

Instructions for reconstitution of the vaccine with diluent (solvent) presented in pre-filled syringe

Qdenga® is a 2-component vaccine that consists of a vial containing lyophilized vaccine and diluent provided in the pre-filled syringe. The lyophilized vaccine must be reconstituted with diluent prior to administration. Remove the vaccine vial and pre-filled syringe diluent from the refrigerator and place at room temperature for approximately 15 minutes. Attach a 23 gauge 1" needle to the pre-filled syringe. Remove the cap from the vaccine vial and clean the surface of stopper on top of the vial using an alcohol wipe. Insert the pre-filled syringe into the lyophilized vaccine vial and slowly inject entire contents. Making sure to keep the vial upright slowly swirl with syringe still inserted into vial, until the vaccine is completely dissolved. Withdraw the entire volume of the reconstituted vaccine. Following reconstitution, the resulting solution should be clear, colorless to pale yellow, and essentially free of foreign particulates. Discard the attached needle and replace with a new 25-gauge 5/8" needle prior to administration.

 Lyophilised Vaccine Vial	 Reconstituted Vaccine	 Reconstituted Vaccine
1. Attach a 23-gauge 1" needle to the pre-filled syringe and insert the needle into the vaccine vial and direct the flow of the diluent toward the side of the vial while slowly depressing the plunger to reduce the chance of forming bubbles	2. Release your finger from the plunger and, holding the assembly on a flat surface, gently swirl the vial in both directions with the needle syringe assembly attached. DO NOT SHAKE. Foam and bubbles may form in the reconstituted product if it is shaken. Let the vial and syringe assembly sit for a while until the solution becomes clear. This takes about 30-60 seconds.	3. Withdraw the entire volume of the reconstituted Qdenga® solution until an air bubble appears in the syringe. Remove the needle syringe assembly from the vial. Hold the syringe with the needle pointing upwards, tap the side of the syringe to bring the air bubble to the top, discard the attached needle and replace with a new 25-gauge 5/8" needle, expel the air bubble until a small drop of the liquid forms at the top of the needle. Qdenga® is ready to be administered by subcutaneous injection.

After reconstitution Qdenga® should be administered immediately. If not used immediately Qdenga® must be used within 2 hours. The reconstituted vaccine can remain in the vial or in the

syringe for this period without loss in potency.

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

HARUS DENGAN RESEP DOKTER

ON MEDICAL PRESCRIPTION ONLY

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi

DNA babi tidak terdeteksi pada produk akhir.

Uji dilakukan oleh laboratorium independen menggunakan metode RT-PCR.

Imported by: PT Takeda Indonesia, Bekasi, Indonesia

Manufactured by: IDT Biologika GmbH, Dessau-Rosslau, Germany, packed and released by Takeda GmbH, Singen, Germany