

Summary of Product Characteristics
QDENGAR[®]
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*: $\geq 3.3 \log_{10}$ PFU**/dose

Live attenuated dengue virus serotype 2#: $\geq 3.1 \log_{10}$ PFU**/dose

Live attenuated dengue virus serotype 3*: $\geq 4.0 \log_{10}$ PFU**/dose

Live attenuated dengue virus serotype 4*: $\geq 4.5 \log_{10}$ 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 for solution for injection.

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

The diluent 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, 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 preceded 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 adult 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.

Qdenga may be administered concomitantly with a human papillomavirus vaccine. This is based on results of a clinical trial involving 307 subjects aged 9 to 14 years who received Qdenga and 9vHPV vaccine concomitantly.

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 vaccination.

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 6-45 years 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 (1-3 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. Vaccine viraemia was detected rarely after the second dose.

Dengue diagnostic tests may be positive during vaccine viremia and cannot be used to distinguish vaccine viremia from wild type dengue infection.

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 12,544 study participants aged 6-45 years (12,098 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 (Table 1) according to the following frequency categories:

Very common: $\geq 1/10$

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

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

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

Very rare: $< 1/10,000$

Table 1: Adverse Reactions From Clinical Studies (Age 6-45 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
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 24.0.

(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.

Note: 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.

Pediatric Population

Pediatric Data in Subjects 6 to 17 Years of Age

Pooled safety data from clinical trials are available for 12,098 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%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 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 4 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, The 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) to receive Qdenga[®] or placebo, regardless of previous dengue infection.

The mean age of the per protocol DEN-301 trial population was 9.6 years (standard deviation of 3.5 years) with 12.7% subjects in the 4-5 years, 55.2% in the 6-11 years and 32.1% in the 12-16 years age-groups. Of these, 46.5% were in Asia and 53.5% were in Latin America, 49.5% were females and 50.5% were males.

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 seronegative rate for the overall per protocol DEN-301 trial population was 27.7%.

Efficacy was assessed using active surveillance across the entire study duration. Any subject with febrile illness (defined as fever $\geq 38^{\circ}\text{C}$ 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 for Subjects 6-16 Years of Age

Efficacy in children aged 6-16 years was assessed in the DEN-301 study which included subjects 4-16 years. 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) ^(a)

	Qdenga [®]	Placebo
Subjects aged 6-11 years		
Number of subjects evaluated	7009	3491
VCD fever, n (%)	34 (0.5)	85 (2.4)
Vaccine efficacy % (95% CI) ^(b)	80.7 (71.3, 87.0)	
Subjects aged 12-16 years		
Number of subjects evaluated	4072	2024
VCD fever, n (%)	14 (0.3)	41 (2.0)
Vaccine efficacy % (95% CI) ^(b)	83.3 (69.4, 90.9)	
Subjects aged 6-16 years		
Number of subjects evaluated	11081	5515
VCD fever, n (%)	48 (0.4)	126 (2.3)
Vaccine efficacy % (95% CI) ^(b)	81.6 (74.3, 86.8)	

CI: confidence interval; n: number of subjects with fever; VCD: virologically confirmed dengue.

(a) The primary analysis of efficacy data was based on the Per Protocol Set, which consisted of all randomized subjects who did not have any major protocol deviations

(b) Vaccine efficacy was defined as $1 - (\lambda_V/\lambda_C)$, where λ_V and λ_C denote the hazard rates for developing VCD fever for the TDV and placebo arms, respectively.

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 Hemorrhagic Fever (DHF). The criteria used in Trial DEN-301 for the assessment of VCD severity by an independent “Dengue Case severity Adjudication Committee” (DCAC) were based on the WHO 2009 guidelines. The DCAC assessed all cases of hospitalization due to VCD utilizing predefined criteria which included an assessment of bleeding abnormality, plasma leakage, liver function, renal function, cardiac function, the central nervous system, and shock. In Trial DEN-301 VCD cases meeting the WHO 1997 criteria for DHF were identified using a programmed algorithm, i.e., without applying medical judgment. Broadly, the criteria included presence of fever lasting 2-7 days, hemorrhagic tendencies, thrombocytopenia, and evidence of plasma leakage.

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

	Qdenga®	Placebo	VE % (95% CI) ^(a)
Subjects aged 6-16 years			
Number of subjects evaluated	11,081	5515	
VE in preventing hospitalizations due to VCD fever, n (%)			
Hospitalizations due to VCD fever	8 (<0.1)	60 (1.1)	93.5 (86.5, 96.9)
VE in preventing VCD fever by dengue serotype, n (%)			
VCD fever caused by DENV-1	26 (0.2)	53 (1.0)	75.8 (61.4, 84.9)
VCD fever caused by DENV-2	7 (<0.1)	73 (1.3)	95.3 (89.8, 97.8)
VCD fever caused by DENV-3	45 (0.4)	43 (0.8)	48.7 (22.1, 66.3)
VCD fever caused by DENV-4	4 (<0.1)	3 (<0.1)	34.3 (-193.6, 85.3)
VE in preventing VCD fever by baseline dengue serostatus, n (%)			
VCD fever in all subjects	82 (0.7)	171 (3.1)	76.8 (69.9, 82.2)
VCD fever in baseline seropositive	57 (0.7)	124 (3.0)	77.9 (69.8, 83.9)
VCD fever in baseline seronegative	25 (0.9)	47 (3.4)	74.4 (58.5, 84.3)
VE in preventing DHF induced by any dengue serotype, n (%)			
Overall	1 (<0.1)	7 (0.1)	92.9 (42.4, 99.1)
VE in preventing severe dengue induced by any dengue serotype, n (%)			
Overall	1 (<0.1)	1 (<0.1)	51.4 (-677.7, 97.0)

CI: confidence interval; n: number of subjects; DENV-1/2/3/4: dengue virus serotype 1/2/3/4; VCD: virologically confirmed dengue; VE: vaccine efficacy.

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

Rapid onset of protection was seen with an exploratory VE of 82.5% (95% CI: 65.1%, 91.2%) against VCD fever caused by all serotypes combined from first vaccination until second vaccination.

2.2 Clinical Efficacy for Subjects 17 to 45 Years of Age

No clinical efficacy study has been conducted in subjects 17-45 years of age. The clinical efficacy of Qdenga® in subjects 17-45 years of age is based on bridging of immunogenicity data from clinical efficacy in subjects 6-16 years of age (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 up to 4.5 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 4.5 Years Post Second Dose in Study DEN-301 (Safety Set) ^(a)

	VE % (95% CI) in Preventing VCD Fever	VE % (95% CI) in Preventing Hospitalization due to VCD Fever
Subjects aged 6-11 years (N = 11,084)		
Overall	63.5 (56.9, 69.1)	85.1 (77.1, 90.3)
By baseline dengue serostatus		
Seropositive	64.8 (57.0, 71.2)	87.8 (78.5, 93.1)
Seronegative	60.5 (46.8, 70.7)	79.1 (59.0, 89.3)
Subjects aged 12-16 years (N = 6435)		
Overall	67.7 (57.8, 75.2)	89.7 (77.9, 95.2)
By baseline dengue serostatus		
Seropositive	68.6 (57.7, 76.7)	89.5 (76.3, 95.4)
Seronegative	63.5 (33.8, 79.9)	90.8 (21.1, 98.8)
Subjects aged 6-16 years (N = 17,519)		
Overall	64.8 (59.4, 69.4)	86.5 (80.3, 90.7)
By baseline dengue serostatus		
Seropositive	66.1 (59.9, 71.3)	88.4 (81.5, 92.7)
Seronegative	61.4 (49.6, 70.4)	81.1 (64.1, 90.0)

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

(a) The Safety Set consisted of all randomized subjects who received at least 1 dose of Qdenga or placebo

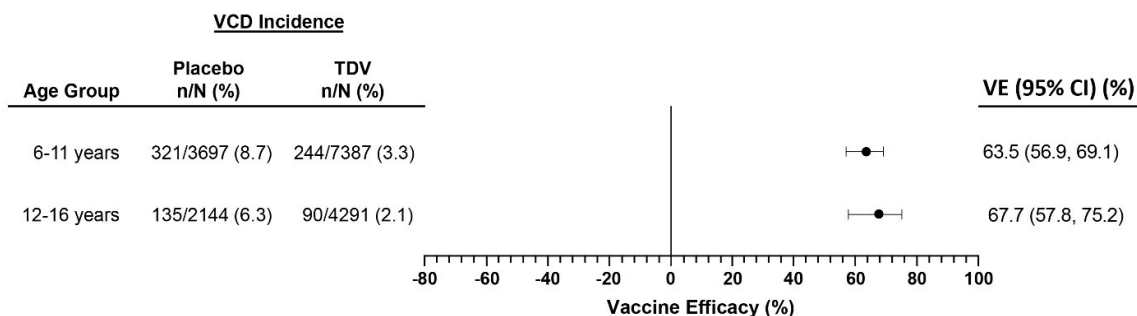
Note: VE was defined as $1 - (\lambda_V / \lambda_C)$, where λ_V and λ_C denote the hazard rates for developing VCD fever for the TDV and placebo arms, respectively.

Additionally, VE in preventing DHF caused by any serotype in subjects aged 6-16 years was 83.3% (95% CI: 54.1%, 93.9%) and in preventing clinically severe VCD cases caused by any serotype was 87.5% (95% CI: -11.7%, 98.6%).

Up to 4.5 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 long-term effect of Qdenga from first dose to 54 months post second dose in different age groups in Trial DEN-301.

Figure 1: Trial DEN-301: Vaccine Efficacy (95% Confidence Interval) and VCD Incidence From First Dose to 54 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; VCD, virologically confirmed dengue; VE, vaccine efficacy.

(a) VE was defined as $1 - (\lambda_V/\lambda_C)$, 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 9 studies with 3877 subjects who received 2 doses of Qdenga® 3 months apart; 2796 of these subjects lived in dengue endemic areas and 1081 subjects lived in non-endemic areas.

Neutralizing antibody titers for each serotype were measured with the microneutralization test (MNT₅₀) 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 MNT₅₀ titer was ≥ 10 (the lower limit of detection [LLOD]), against at least one serotype.
- Dengue seronegative if the MNT₅₀ titer was $<$ the LLOD against all 4 serotypes.

3.1 Immunogenicity Data for Subjects 6-16 Years of Age

The immunogenicity of Qdenga® in children aged 6-16 years was assessed in Trial DEN-301 which included subjects aged 4-16 years. The GMTs by baseline dengue serostatus in subjects aged 6-11, 12-16 and 6-16 years of age are shown in Table 5.

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

	GMT (95% CI)			
	Baseline Seropositive		Baseline Seronegative	
	Pre-Vaccination	1 Month Post Dose 2	Pre-Vaccination	1 Month Post Dose 2
Subjects aged 6-11 years				
Number of subjects evaluated	953	838	433	394
DENV-1	320.9 (272.5, 377.8)	1900.8 (1700.6, 2124.6)	5.0 NE ^(b)	173.4 (154.7, 194.2)
DENV-2	611.2 (531.9, 702.4)	4827.7 (4498.7, 5180.8)	5.0 NE ^(b)	1678.7 (1533.5, 1837.7)
DENV-3	260.4 (224.1, 302.6)	1549.9 (1415.4, 1697.3)	5.0 NE ^(b)	234.9 (213.8, 258.1)
DENV-4	177.0 (154.5, 202.9)	1033.7 (953.7, 1120.3)	5.0 NE ^(b)	145.1 (132.5, 159.0)
Subjects aged 12-16 years				
Number of subjects evaluated	679	614	137	124
DENV-1	744.6 (622.2, 891.1)	2713.3 (2407.0, 3058.6)	5.0 NE ^(b)	177.2 (144.6, 217.1)
DENV-2	1282.7 (1096.0, 1501.2)	5572.2 (5115.4, 6069.7)	5.0 NE ^(b)	2208.8 (1876.0, 2600.7)
DENV-3	690.5 (589.1, 809.4)	2314.6 (2080.1, 2575.5)	5.0 NE ^(b)	211.1 (174.4, 255.6)
DENV-4	353.5 (305.1, 409.6)	1353.7 (1237.7, 1480.7)	5.0 NE ^(b)	135.4 (112.1, 163.5)
Subjects aged 6-16 years				
Number of subjects evaluated	1632	1452	570	518
DENV-1	455.5 (402.9, 514.9)	2209.5 (2035.1, 2398.9)	5.0 NE ^(b)	174.3 (157.9, 192.4)
DENV-2	831.8 (748.4, 924.5)	5129.5 (4857.3, 5417.0)	5.0 NE ^(b)	1792.7 (1655.6, 1941.1)
DENV-3	390.6 (349.1, 436.9)	1836.4 (1712.5, 1969.2)	5.0 NE ^(b)	229.0 (210.4, 249.2)
DENV-4	236.1 (213.2, 261.4)	1158.6 (1090.8, 1230.5)	5.0 NE ^(b)	142.7 (131.5, 155.0)

CI: confidence interval; DENV-1/2/3/4: dengue virus serotype 1/2/3/4; GMT: geometric mean titer; NE: not estimated.

(a) The immunogenicity subset was a randomly selected subset of subjects, and the Per Protocol Set for Immunogenicity was the collection of subjects from that subset who also belong to the Per Protocol Set.

(b) All subjects had GMT values below the lower limit of detection (10), hence were reported as 5 with no CI values.

3.2 Immunogenicity Data for Subjects 18-45 Years of Age

The immunogenicity of Qdenga[®] in adults 18-45 years of age was assessed in DEN-304, a Phase 3 double-blind, randomized, placebo-controlled study which included subjects 18-60 years of age from a non-endemic country (US). The post-dose 2 GMTs are shown in Table 6a for baseline seronegative subjects and Table 6b for baseline seropositive subjects.

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

	GMT (95% CI)			
	Age 18-30 Years		Age 31-45 Years	
	Pre-Vaccination	1 Month Post Dose 2	Pre-Vaccination	1 Month Post Dose 2
Number of subjects evaluated	94	91	125	119
DENV-1	5.0 NE ^(a)	251.1 (190.8, 330.6)	5.0 NE ^(a)	245.7 (181.1, 333.3)
DENV-2	5.0 NE ^(a)	2575.6 (2008.1, 3303.4)	5.0 NE ^(a)	3298.3 (2743.6, 3965.3)
DENV-3	5.0 NE ^(a)	106.9 (84.5, 135.3)	5.0 NE ^(a)	131.6 (101.2, 171.1)
DENV-4	5.0 NE ^(a)	123.0 (101.4, 149.3)	5.0 NE ^(a)	141.9 (111.5, 180.5)

CI: confidence interval; DENV-1/2/3/4: dengue virus serotype 1/2/3/4; GMT: geometric mean titer; NE: not estimated.

(a) Not estimated since no measure of variance is available (all GMT values were below the lower limit of detection (10) and an imputed value (5) was applied to all subjects).

Note: Pooled data from dengue tetravalent vaccine Lots 1, 2 and 3.

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

	GMT (95% CI)			
	Age 18-30 Years		Age 31-45 Years	
	Pre-Vaccination	1 Month Post Dose 2	Pre-Vaccination	1 Month Post Dose 2
Number of subjects evaluated	15	14	28	28
DENV-1	13.6 (6.2, 30.0)	333.3 (104.3, 1065.2)	9.6 (5.9, 15.5)	288.5 (155.8, 534.4)
DENV-2	35.0 (16.5, 74.4)	2786.7 (996.7, 7791.3)	27.5 (18.6, 40.5)	3674.6 (2361.4, 5717.9)
DENV-3	7.1 (4.2, 12.1)	171.5 (71.0, 414.1)	5.7 (4.7, 7.0)	162.8 (81.4, 325.4)
DENV-4	7.1 (4.2, 12.1)	187.8 (59.8, 589.8)	5.0 NE ^(a)	196.8 (104.4, 371.1)

CI: confidence interval; DENV-1/2/3/4: dengue virus serotype 1/2/3/4; GMT: geometric mean titer; NE: not estimated.

(a) Not estimated since no measure of variance is available (all GMT values were below the lower limit of detection (10) and an imputed value (5) was applied to all subjects).

Note: Pooled data from dengue tetravalent vaccine Lots 1, 2 and 3.

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 (6-16 Years) and DEN-304 (18-45 Years) (Per Protocol Set for Immunogenicity)

	GMT Ratio ^(a) (95% CI)			
	DENV-1	DENV-2	DENV-3	DENV-4
Post-hoc analysis in subjects aged 6-16 and 18-45 years				
1 month post-2 nd dose	0.70 (0.57, 0.86)	0.61 (0.52, 0.71)	1.90 (1.60, 2.27)	1.07 (0.91, 1.26)
6 months post-2 nd dose	0.78 (0.62, 0.98)	0.77 (0.65, 0.93)	1.21 (1.01, 1.46)	1.24 (1.03, 1.50)

CI: confidence interval, DENV-1/2/3/4: dengue virus serotype 1/2/3/4; GMT: geometric mean titer.

(a) Non-inferiority: upper bound of the 95% CI of the GMT ratio of GMTs in 6-16 years old and GMTs in 18-45 years old is <2.0.

3.3 Long-term Persistence of Antibodies

The long-term persistence of neutralizing antibodies was shown in Study DEN-301, with titers remaining well above the pre-vaccination levels for all four serotypes, up to 51 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:

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 provided.

6.3 Stability After Reconstitution

After reconstitution with the diluent provided:

Qdenga[®] should be used immediately.

If not used immediately Qdenga[®] must be used within 2 hours from reconstitution.

Chemical and physical in-use stability have been demonstrated for 2 hours at room temperature (up to 32.5°C) from the time of reconstitution of the vaccine vial. After this time period, the vaccine must be discarded. Do not return it to the refrigerator.

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 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 in glass vial (Type-I glass), with a stopper (bromobutyl rubber) and aluminum seal with purple flip-off plastic cap:
 - Pack size of 1 : DK12264500244A1
 - Pack size of 10 : DK12264500244A1

Qdenga[®] powder and diluent 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 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 : DK12264500244A1
 - Pack size of 5 : DK12264500244A1

Not all pack sizes may be marketed.

6.6 Instructions for Use/Handling

Instructions for reconstitution of the vaccine with the diluent presented in vial

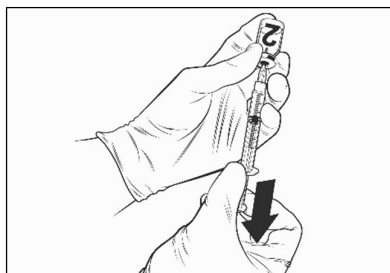
Qdenga is a 2-component vaccine that consists of a vial containing lyophilized vaccine and a vial containing diluent. The lyophilized vaccine must be reconstituted with diluent prior to administration.

Use only sterile syringes for reconstitution and injection of Qdenga. Qdenga should not be mixed with other vaccines in the same syringe.

To reconstitute Qdenga, use only the diluent (0.22% sodium chloride solution) supplied with the vaccine since it is free of preservatives or other anti-viral substances. Contact with

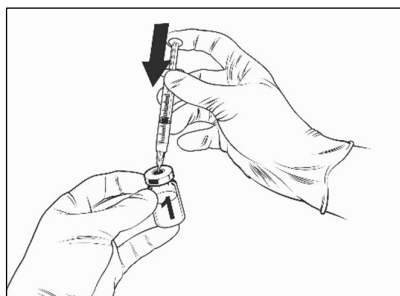
preservatives, antiseptics, detergents, and other anti-viral substances is to be avoided since they may inactivate the vaccine.

Remove the vaccine and diluent vials from the refrigerator and place at room temperature for approximately 15 minutes.



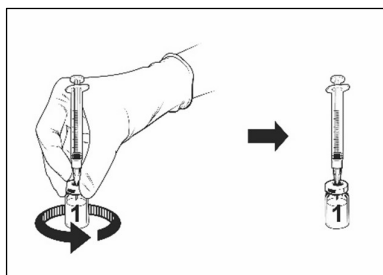
Diluent vial

- Remove the caps from both vials and clean the surface of stoppers on top of the vials using an alcohol wipe.
- Attach a sterile needle to a sterile 1 mL syringe and insert the needle into the diluent vial. The recommended needle is 23G.
- 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.
- Remove the needle syringe assembly from the diluent vial.
- Invert the syringe to bring the bubble back to the plunger.



Lyophilized vaccine vial

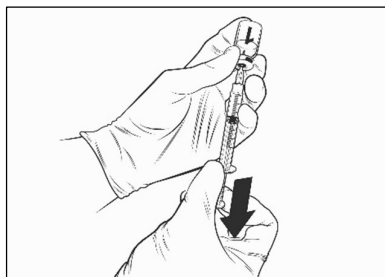
- Insert the needle of the syringe assembly into the lyophilized vaccine vial.
- Direct the flow of the diluent toward the side of the vial while slowly depressing the plunger to reduce the chance of forming bubbles.



Reconstituted vaccine

- 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.
- Let the vial and syringe assembly sit for a while until the solution becomes clear. This takes about 30-60 seconds.

Following reconstitution, the resulting solution should be clear, colorless to pale yellow, and essentially free of foreign particulates. Discard the vaccine if particulates are present and/or if it appears discolored.



Reconstituted vaccine

- Withdraw the entire volume of the reconstituted Qdenga solution with the same syringe 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 sterile needle, expel the air bubble until a small drop of the liquid forms at the top of the needle. The recommended needle is 25G 16 mm.
- Qdenga is ready to be administered by subcutaneous injection.

Qdenga should be administered immediately after reconstitution. Chemical and physical in-use stability have been demonstrated for 2 hours at room temperature (up to 32.5°C) from the time of reconstitution of the vaccine vial. After this time period, the vaccine must be discarded. Do not return it to the refrigerator.

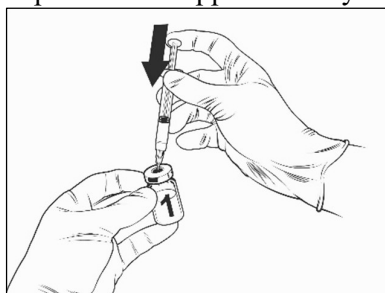
Instructions for reconstitution of the vaccine with diluent presented in pre-filled syringe

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.

Qdenga should not be mixed with other vaccines in the same syringe.

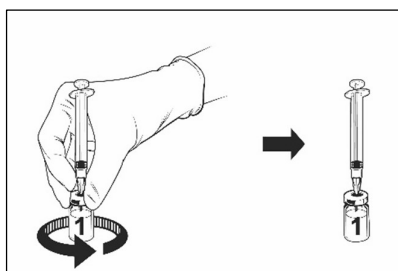
To reconstitute Qdenga, use only the diluent (0.22% sodium chloride solution) in the pre-filled syringe supplied with the vaccine since it is free of preservatives or other anti-viral substances. Contact with preservatives, antiseptics, detergents, and other anti-viral substances is to be avoided since they may inactivate the vaccine.

Remove the vaccine vial and pre-filled syringe diluent from the refrigerator and place at room temperature for approximately 15 minutes.



Lyophilized vaccine vial

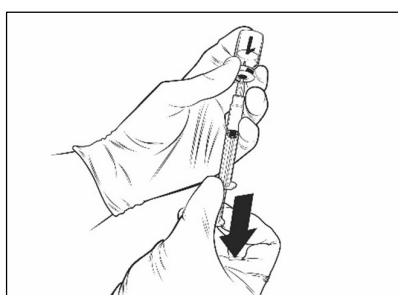
- Remove the cap from the vaccine vial and clean the surface of stopper on top of the vial using an alcohol wipe.
- Attach a sterile needle to the pre-filled syringe and insert the needle into the vaccine vial. The recommended needle is 23G.
- Direct the flow of the diluent toward the side of the vial while slowly depressing the plunger to reduce the chance of forming bubbles.



Reconstituted vaccine

- 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.
- Let the vial and syringe assembly sit for a while until the solution becomes clear. This takes about 30-60 seconds.

Following reconstitution, the resulting solution should be clear, colorless to pale yellow, and essentially free of foreign particulates. Discard the vaccine if particulates are present and/or if it appears discolored.



Reconstituted vaccine

- Withdraw the entire volume of the reconstituted Qdenga solution with the same syringe 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 sterile needle, expel the air bubble until a small drop of the liquid forms at the top of the needle. The recommended needle is 25G 16 mm.
- Qdenga is ready to be administered by subcutaneous injection.

Qdenga should be administered immediately after reconstitution. Chemical and physical in-use stability have been demonstrated for 2 hours at room temperature (up to 32.5°C) from the time of reconstitution of the vaccine vial. After this time period, the vaccine must be discarded. Do not return it to the refrigerator.

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.



Marketing Authorization Holder: PT Tunggal Idaman Abdi, Jakarta, Indonesia

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

Informasi untuk Pengguna

Qdenga[®], serbuk dan pelarut untuk larutan injeksi **Qdenga[®], serbuk dan pelarut untuk larutan injeksi dalam *pre-filled syringe***

Vaksin dengue tetravalen (hidup, dilemahkan)

Bacalah keseluruhan brosur ini dengan seksama sebelum anda atau anak anda menggunakan vaksin ini, karena brosur ini berisi informasi penting untuk anda.

- Simpan brosur ini. Mungkin diperlukan untuk dibaca kembali.
- Jika anda memiliki pertanyaan lebih lanjut, hubungi dokter, apoteker atau perawat
- Vaksin ini diresepkan untuk anda atau anak anda. Jangan berikan pada orang lain.
- Jika ada efek samping pada anda atau anak anda, bicarakan dengan dokter, apoteker atau perawat. Hal ini termasuk kemungkinan efek samping apapun yang tidak tercantum dalam brosur ini. Lihat pada bagian 4.

Apa isi brosur ini:

1. Apa yang dimaksud dengan Qdenga[®] dan kegunaannya
2. Apa yang perlu diketahui mengenai Qdenga[®] sebelum diberikan pada anda atau anak anda.
3. Cara menggunakan Qdenga[®]
4. Efek samping yang mungkin terjadi
5. Cara menyimpan Qdenga[®]
6. Isi kemasan dan informasi lainnya

1. Apa yang dimaksud dengan Qdenga[®] dan kegunaannya

Qdenga[®] adalah vaksin yang digunakan untuk melindungi anda dari penyakit dengue yang disebabkan oleh virus dengue serotipe 1, 2, 3 dan 4. Qdenga[®] berisi keempat serotipe virus dengue yang sudah dilemahkan sehingga tidak dapat menyebabkan penyakit dengue.

Qdenga[®] diberikan untuk anak, remaja dan dewasa usia 6 sampai 45 tahun.

Qdenga[®] harus digunakan sesuai rekomendasi resmi.

Cara kerja Qdenga[®]

Qdenga[®] menstimulasi pertahanan alami tubuh (sistem kekebalan tubuh) yang akan membantu melindungi dari virus yang dapat menyebabkan penyakit dengue bila tubuh kita terpapar virus dengue di waktu mendatang.

Yang dimaksud dengan penyakit dengue

Penyakit dengue disebabkan oleh virus.

- Virus ini disebarkan oleh nyamuk (nyamuk *Aedes*) yang terinfeksi virus dengue
- Bila seekor nyamuk menggigit seseorang dengan penyakit dengue maka penyakit ini dapat menular ke orang yang digigit berikutnya.

Penyakit dengue tidak menular langsung dari orang ke orang.

Gejala penyakit dengue mencakup demam, sakit kepala, nyeri di belakang mata, nyeri otot dan sendi, rasa mual dan muntah, pembengkakan pada kelenjar atau kemerahan pada kulit. Gejala penyakit dengue biasanya berlangsung 2 sampai 7 hari, namun juga bisa tanpa gejala.

Kadang-kadang penyakit dengue bisa cukup berat sehingga harus dirawat di rumah sakit, dan walaupun jarang terjadi, dapat menyebabkan kematian. Penyakit dengue berat dapat menyebabkan demam tinggi atau gejala berikut: nyeri perut yang parah, muntah yang terus menerus, perdarahan

berat, perdarahan di lambung, gusi berdarah, merasa lelah, merasa gelisah, koma (kehilangan kesadaran), mengalami kejang dan kegagalan organ.

2. Apa yang perlu diketahui mengenai Qdenga® sebelum diberikan pada anda atau anak anda

Untuk memastikan Qdenga® cocok untuk anda atau anak anda, penting untuk menyampaikan pada dokter, apoteker atau perawat bila hal-hal di bawah ini terjadi pada anda atau anak anda. Bila ada yang tidak anda pahami, tanyakan pada dokter, apoteker atau perawat untuk menjelaskan pada anda.

Jangan gunakan Qdenga® bila anda atau anak anda:

- Alergi terhadap komponen aktif atau komponen lain dari Qdenga® yang tercantum pada bagian 6.
- Sebelumnya pernah mengalami reaksi alergi setelah menerima Qdenga®. Reaksi alergi dapat ditandai dengan ruam yang gatal, sesak nafas, dan pembengkakan di wajah atau lidah.
- Memiliki sistem kekebalan tubuh yang lemah. Ini dapat disebabkan antara lain karena cacat genetik atau infeksi HIV.
- Sedang menerima obat yang mempengaruhi sistem imun (seperti kortikosteroid dosis tinggi atau kemoterapi). Dokter anda tidak akan memberikan Qdenga® sampai 4 minggu setelah anda menghentikan pengobatan tersebut.
- Hamil
- Menyusui

Peringatan dan Perhatian

Beritahukan dokter, apoteker atau perawat sebelum menerima Qdenga® bila anda atau anak anda:

- Mengalami infeksi disertai demam. Mungkin perlu menunda vaksinasi sampai anda atau anak anda pulih.
- Pernah mengalami masalah kesehatan setelah menerima vaksin. Dokter anda akan secara hati-hati mempertimbangkan risiko dan manfaat vaksinasi.
- Pernah pingsan akibat injeksi. Pusing, pingsan, dan kadang jatuh, dapat terjadi (kebanyakan pada orang muda) setelah, atau bahkan sebelum menerima injeksi.

Informasi penting tentang perlindungan yang diberikan oleh vaksin ini

Sebagaimana vaksin lain, Qdenga® mungkin tidak melindungi semua orang yang menerimanya dan perlindungan mungkin berkurang seiring waktu. Anda masih mungkin mengalami demam dengue akibat gigitan nyamuk, termasuk penyakit dengue parah. Anda harus terus melindungi anda atau anak anda dari gigitan nyamuk bahkan setelah vaksinasi dengan Qdenga®.

Setelah vaksinasi, konsultasikan dengan dokter bila anda atau anak anda terinfeksi dengue dan mengalami gejala berikut: demam tinggi, nyeri perut parah, muntah yang menerus, nafas cepat, gusi berdarah, merasa lelah, gelisah dan muntah darah.

Tindakan pencegahan untuk perlindungan tambahan

Anda perlu melakukan tindakan pencegahan gigitan nyamuk, seperti penggunaan penolak nyamuk, pakaian yang lebih melindungi, dan kelambu.

Qdenga® dan penggunaan obat lain

Qdenga® dapat digunakan bersama vaksin hepatitis A, vaksin demam kuning (*yellow fever*) atau vaksin *human papillomavirus* (HPV) dengan tempat injeksi terpisah (bagian lain dari tubuh anda, biasanya pada lengan yang lain) pada kunjungan yang sama. Penggunaan Qdenga® bersamaan dengan vaksin hepatitis A atau vaksin demam kuning (*yellow fever*) telah diteliti pada orang dewasa. Penggunaan Qdenga® bersamaan dengan vaksin *human papillomavirus* (HPV) telah diteliti pada anak.

Beritahukan dokter atau apoteker bila anda atau anak anda sedang menggunakan, atau baru menggunakan, atau mungkin menggunakan vaksin atau obat lain.

Secara khusus, beritahukan dokter atau apoteker bila anda atau anak anda menerima salah satu dari:

- Obat yang mempengaruhi perlindungan alami tubuh (sistem kekebalan tubuh) seperti kortikosteroid dosis tinggi atau kemoterapi. Pada kasus ini, dokter anda tidak akan memberikan Qdenga® sampai 4 minggu setelah anda menghentikan penggunaan obat tersebut. Ini dilakukan karena Qdenga® mungkin tidak bekerja sebaik yang diharapkan.
- Obat yang disebut immunoglobulin atau produk darah yang mengandung immunoglobulin, seperti darah atau plasma. Dalam kasus ini, dokter anda tidak akan memberikan Qdenga® sampai 6 minggu (sebaiknya tidak lebih dari 3 bulan) setelah anda menghentikan pengobatan. Ini dilakukan karena Qdenga® mungkin tidak bekerja sebaik yang diharapkan.

Kehamilan dan menyusui

Jangan menggunakan Qdenga® bila anda atau putri anda sedang hamil atau menyusui.

Bila anda atau putri anda:

- berada pada masa usia subur, anda harus mengambil tindakan pencegahan yang diperlukan untuk mencegah kehamilan selama 1 bulan setelah menerima Qdenga®.
- menduga anda atau putri anda mungkin sedang hamil atau berencana untuk hamil, mintakan saran pada dokter, apoteker atau perawat sebelum menerima Qdenga®.

Mengemudi dan menggunakan mesin

Qdenga® memiliki pengaruh minor terhadap kemampuan mengemudi dan menggunakan mesin pada beberapa hari pertama setelah vaksinasi.

3. Cara pemberian Qdenga®

Qdenga® diberikan oleh dokter atau perawat melalui injeksi di bawah kulit (subkutan) di lengan atas. Vaksin ini tidak boleh diinjeksi ke dalam pembuluh darah, ke dalam kulit atau ke dalam otot.

Anda atau anak anda akan menerima 2 injeksi. Injeksi kedua diberikan 3 bulan setelah injeksi pertama.

Qdenga® harus diberikan sesuai rekomendasi resmi.

Instruksi penyiapan (rekonstitusi) vaksin yang ditujukan untuk profesional medis dan kesehatan tersedia di bagian akhir brosur.

Bila jadwal pemberian Qdenga® terlewat/terlupa

- Bila anda atau anak anda melewatkan jadwal vaksinasi, dokter anda akan memutuskan kapan dosis yang terlewat tersebut akan diberikan. Penting untuk anda atau anak anda untuk mengikuti instruksi yang diberikan dokter, apoteker atau perawat anda tentang jadwal vaksinasi.
- Bila anda lupa atau tidak bisa kembali sesuai jadwal yang direncanakan, mintakan saran ke dokter, apoteker atau perawat anda.
- Jika anda memiliki pertanyaan lebih jauh tentang penggunaan vaksin ini, tanyakan ke dokter, apoteker atau perawat.

4. Efek samping yang mungkin terjadi

Sebagaimana obat lainnya, Qdenga® dapat menyebabkan efek samping, walaupun tidak semua penerima vaksin mengalaminya.

Efek samping berikut ini terjadi selama penelitian pada anak, orang muda dan dewasa (usia 6 sampai 45 tahun):

Sangat umum (dapat terjadi pada lebih dari 1 orang di antara 10 orang):

- Nyeri di tempat injeksi
- Sakit kepala

- Nyeri otot
- Memerah di tempat injeksi
- Secara umum merasa tidak enak badan
- Merasa lemah
- Infeksi pada hidung atau tenggorokan
- Demam

Umum (dapat terjadi pada 1 di antara 10 orang)

- Pembengkakan di tempat injeksi
- Nyeri atau radang hidung atau tenggorokan
- Memar di tempat injeksi
- Gatal di tempat injeksi
- Radang pada tenggorokan dan amandel
- Nyeri sendi
- Penyakit menyerupai influenza

Tidak umum (dapat terjadi pada 1 di antara 100 orang)

- Nyeri perut
- Diare
- Mual
- Muntah
- Perdarahan di tempat injeksi
- Pusing
- Kulit gatal
- Ruam kulit, termasuk ruam akibat virus, bintik-bintik merah kecil, dan ruam gatal
- Peradangan saluran nafas
- Pilek
- Biduran

Sangat jarang (dapat terjadi pada 1 di antara 10.000 orang)

- pembengkakan cepat di bawah kulit di area seperti wajah, tenggorokan, lengan, dan kaki

Pelaporan efek samping

Jika anda mengalami efek samping, bicarakan dengan dokter, apoteker atau perawat. Ini mencakup efek samping lain yang tidak tercantum dalam brosur. Dengan melaporkan efek samping, anda dapat membantu penyediaan informasi keamanan vaksin ini.

5. Cara menyimpan Qdenga®

Simpan Qdenga® jauh dari jangkauan dan penglihatan anak-anak.

Jangan gunakan Qdenga® setelah tanggal kadaluarsa yang tertera pada dus (EXP). Tanggal kadaluarsa mengacu pada hari terakhir bulan tersebut.

Simpan di lemari pendingin (2°C sampai 8°C)

Jangan dibekukan. Simpan vaksin dalam dusnya.

Setelah mencampur (rekonstitusi) vaksin dengan pelarut yang disediakan, Qdenga® harus digunakan segera. Bila tidak segera digunakan Qdenga® harus digunakan dalam 2 jam.

Jangan buang obat ke dalam saluran limbah air atau saluran limbah rumah tangga. Tanyakan apoteker bagaimana membuang obat yang tidak lagi digunakan. Tindakan ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

Isi Qdenga[®]

- Setelah rekonstitusi, satu dosis (0.5 mL) mengandung
 - Virus dengue hidup yang dilemahkan serotipe 1*: $\geq 3,3 \log_{10}$ PFU**
 - Virus dengue hidup yang dilemahkan serotipe 2#: $\geq 3,1 \log_{10}$ PFU**
 - Virus dengue hidup yang dilemahkan serotipe 3*: $\geq 4,0 \log_{10}$ PFU**
 - Virus dengue hidup yang dilemahkan serotipe 4*: $\geq 4,5 \log_{10}$ PFU**

* diproduksi dalam sel Vero menggunakan teknologi DNA rekombinan. Gen protein permukaan spesifik-serotipe direkayasa ke dalam *backbone* dengue tipe 2

#Diproduksi dalam sel Vero menggunakan teknologi DNA rekombinan.

**PFU=Plaque-forming units

- Kandungan lainnya: α, α -trehalosa dihidrat, Poloxamer 407, *human serum albumin*, kalium dihidrogen fosfat, dinatrium hidrogen fosfat, kalium klorida, natrium klorida, air untuk injeksi

Tampilan Qdenga[®] dan isi kemasan

Qdenga[®] adalah serbuk dan pelarut untuk larutan injeksi. Qdenga[®] tersedia dalam bentuk:

- serbuk dalam satu vial dosis tunggal dan pelarut dalam satu vial dosis tunggal.
- serbuk dalam satu vial dosis tunggal dan pelarut dalam satu *prefilled syringe* dengan 2 jarum terpisah.

Serbuk dan pelarut harus dicampur sebelum digunakan.

Qdenga[®], serbuk dan pelarut untuk larutan injeksi tersedia dalam kemasan isi 1 atau isi 10:

- kemasan isi 1: Reg. No. DK12264500244A1
- kemasan isi 10: Reg. No. DK12264500244A1

Qdenga[®], serbuk dan pelarut untuk larutan injeksi dalam *pre-filled syringe* tersedia dalam kemasan isi 1 atau isi 5:

- kemasan isi 1: Reg. No. DK12264500244A1
- kemasan isi 5: Reg. No. DK12264500244A1

Tidak semua kemasan mungkin akan dipasarkan di Indonesia.

Serbuk berupa serbuk padat berwarna putih sampai putih pucat.

Pelarut (larutan natrium klorida 0.22%) berupa cairan jernih tanpa warna.

Setelah rekonstitusi, Qdenga[®] berupa larutan jernih, tanpa warna sampai kuning pucat, dan bebas dari partikel asing.

Diproduksi oleh: IDT Biologika GmbH, Dessau Rosslau, Jerman, dikemas dan di-*release* oleh Takeda GmbH, Singen, Jerman.

Pemegang ijin edar: PT Tunggal Idaman Abdi, Jakarta, Indonesia
HARUS DENGAN RESEP DOKTER

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi.

DNA babi tidak terdeteksi pada produk akhir.

Uji dilakukan oleh laboratorium independen menggunakan metode RT-PCR.

Informasi berikut hanya dimaksudkan untuk professional kesehatan:

- Sebagaimana dengan vaksin injeksi lainnya, pengobatan medis dan pengawasan yang tepat harus segera tersedia bila terjadi reaksi anafilaksis setelah pemberian Qdenga®.
- Qdenga® tidak boleh dicampur dengan obat atau vaksin lain dalam satu syringe.
- Qdenga® tidak boleh diberikan secara intravena, intrakutan atau intramuskular dalam keadaan apapun.
- Imunisasi harus diberikan secara subkutan, sebaiknya pada lengan atas di daerah deltoid.
- Pingsan dapat terjadi setelah, atau bahkan sebelum, vaksinasi apapun sebagai respons psikogenik terhadap injeksi menggunakan jarum. Prosedur harus tersedia untuk mencegah cedera jatuh dan untuk menangani reaksi pingsan.

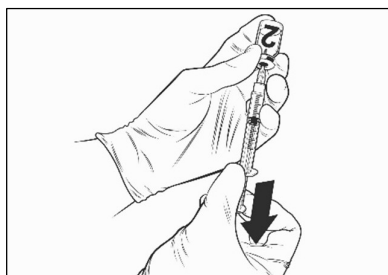
Petunjuk rekonstitusi vaksin dengan pelarut yang terdapat di dalam vial:

Qdenga® adalah vaksin dengan 2 komponen yang terdiri dari vial yang berisi vaksin terliofilisasi dan vial yang berisi pelarut. Vaksin terliofilisasi harus direkonstitusi dengan pelarut sebelum diberikan.

Hanya gunakan syringe steril untuk rekonstitusi dan injeksi Qdenga®. Qdenga® tidak boleh dicampur dengan vaksin lain dalam satu syringe.

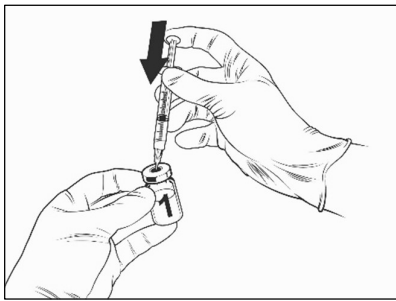
Untuk merekonstitusi Qdenga®, hanya gunakan pelarut (larutan natrium klorida 0,22%) yang disertakan bersama vaksin karena bebas dari bahan pengawet atau zat antivirus lainnya. Sentuhan dengan bahan pengawet, antiseptik, detergen, dan zat antivirus lainnya harus dihindari karena dapat menyebabkan vaksin tidak aktif.

Keluarkan vial vaksin dan vial pelarut dari dalam lemari pendingin dan tempatkan di suhu ruang selama sekitar 15 menit.



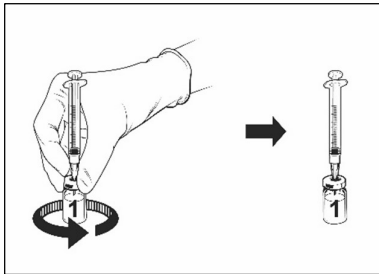
Vial pelarut

- Lepaskan sungkup kedua vial dan bersihkan permukaan sumbat di bagian atas vial dengan menggunakan tisu alkohol.
- Pasang jarum steril ke *syringe* steril 1 ml dan tusukkan jarum ke vial pelarut. Jarum yang direkomendasikan adalah jarum 23G.
- Tekan plunger perlahan sepenuhnya ke bawah.
- Balik vial dengan bagian atas menghadap ke bawah, keluarkan seluruh isi vial dan terus menarik plunger hingga mencapai 0,75 ml. Akan terlihat ada gelembung di dalam *syringe*.
- Lepaskan syringe (dengan jarum) dari vial pelarut
- Balik *syringe* untuk membawa gelembung kembali ke plunger.



Vial vaksin terlio-filisasi

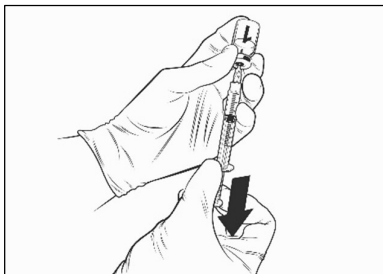
- Masukkan jarum *syringe* ke dalam vial vaksin terlio-filisasi.
- Arahkan aliran pelarut ke dinding dalam vial sambil menekan plunger perlahan untuk mengurangi kemungkinan terbentuknya gelembung.



Vaksin yang direkonstitusi

- Lepaskan jari Anda dari plunger dan, dengan memegang *syringe* bersama vial di atas permukaan yang rata, aduk isi vial dengan membuat gerakan memutar perlahan ke kedua arah dengan jarum alat suntik tetap terpasang.
- JANGAN DIKOCOK. Busa dan gelembung udara mungkin terbentuk dalam produk yang direkonstitusi.
- Biarkan vial dan *syringe* sejenak hingga larutan menjadi jernih. Langkah ini membutuhkan waktu sekitar 30-60 detik.

Setelah rekonstitusi, larutan yang dihasilkan haruslah jernih, tidak berwarna hingga kuning pucat, dan tidak mengandung partikulat asing. Buang vaksin jika terdapat partikel dan/atau jika warnanya berubah.



Vaksin yang direkonstitusi

- Ambil seluruh volume larutan Qdenga® yang telah direkonstitusi dengan *syringe* yang sama hingga gelembung udara muncul di dalam *syringe*.
- Lepaskan *syringe* dari vial.
- Pegang *syringe* dengan jarum mengarah ke atas, ketuk-ketuk bagian samping *syringe* untuk membawa gelembung udara ke atas, lepaskan dan buang jarum yang terpasang dan ganti dengan jarum steril baru, keluarkan gelembung udara hingga setetes kecil cairan terbentuk di ujung jarum. Jarum yang direkomendasikan adalah 25G 16 mm.
- Qdenga® siap untuk diberikan melalui injeksi subkutan.

Setelah direkonstitusi, Qdenga® harus segera diberikan. Stabilitas kimia dan fisik dalam penggunaan telah ditunjukkan selama 2 jam pada suhu ruang (hingga 32,5 °C) sejak rekonstitusi vial vaksin. Lewat dari waktu tersebut, vaksin harus dibuang. Janganembalikan ke dalam lemari pendingin.

Setiap produk yang tidak terpakai atau bahan limbah harus dibuang sesuai dengan peraturan setempat.

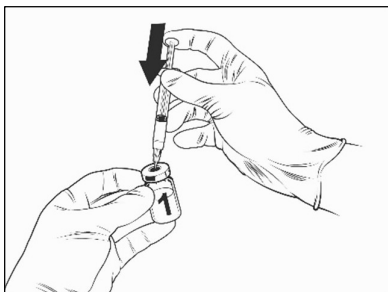
Petunjuk rekonstitusi vaksin dengan pelarut yang terdapat di dalam *pre-filled syringe*

Qdenga® adalah vaksin 2 komponen yang terdiri dari vial yang berisi vaksin terlio-filisasi dan pelarut yang disediakan dalam *pre-filled syringe*. Vaksin terlio-filisasi harus direkonstitusi dengan pelarut sebelum diberikan.

Qdenga® tidak boleh dicampur dengan vaksin lain dalam alat suntik yang sama.

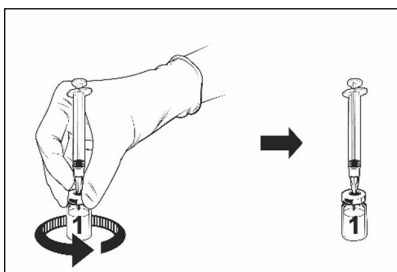
Untuk merekonstitusi Qdenga®, hanya gunakan pelarut (larutan natrium klorida 0,22%) dalam *pre-filled syringe* yang disertakan bersama vaksin karena bebas dari bahan pengawet atau zat antivirus lainnya. Sentuhan dengan bahan pengawet, antiseptik, detergen, dan zat antivirus lainnya harus dihindari karena dapat menyebabkan vaksin tidak aktif.

Keluarkan vial vaksin dan pelarut di dalam *pre-filled syringe* dari dalam lemari pendingin dan tempatkan di suhu ruang selama sekitar 15 menit.



Vial vaksin terlioofilisasi

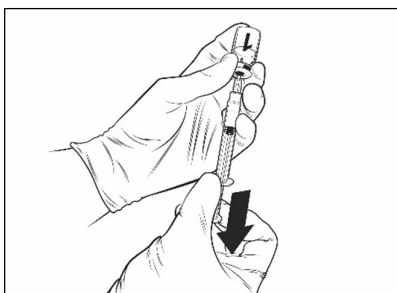
- Lepaskan sungkup vial vaksin dan bersihkan permukaan sumbat di bagian atas vial dengan menggunakan tisu alkohol.
- Pasang jarum steril ke *pre-filled syringe* dan tusukkan jarum ke vial vaksin. Jarum yang direkomendasikan adalah 23G.
- Arahkan aliran pelarut ke dinding dalam vial sambil menekan plunger perlahan untuk mengurangi kemungkinan terbentuknya gelembung.



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