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:

Dengue virus serotype 1 (live, attenuated)*: ≥ 3.3 log10 PFU**/dose

Dengue virus serotype 2 (live, attenuated)#: ≥ 2.7 log10 PFU**/dose

Dengue virus serotype 3 (live, attenuated)*: ≥ 4.0 log10 PFU**/dose

Dengue virus serotype 4 (live, attenuated)*: ≥ 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 4 years to 60 years of age.

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

4.2 Posology and Method of Administration

Dosage

Individuals 4 years to 60 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

Elderly Patients

The safety and efficacy of Qdenga in subjects above 60 years of age has not been established.

Pediatric Patients

The safety and efficacy of Qdenga in children aged less than 4 years has not yet been established. Currently available data are described in section 4.8 but no recommendation on a posology can be made.

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.

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 other 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. 20mg/day or 2mg/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

Events of anaphylaxis have been reported post authorization.

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.

There are no data on the use of Qdenga in subjects above 60 years of age and limited data in patients with chronic medical conditions.

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. 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.

Coadministration has been studied in subjects aged 9 to 14 years.

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 4 to 60 years of age were injection site pain (50%), headache (35%), myalgia (31%), injection site erythema (27%), malaise (24%), asthenia (20%) and fever (11%). 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. Vaccine viremia 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 and post-authorization experience are tabulated below.

The safety profile presented below is based on data generated in placebo-controlled clinical studies and post-authorization experience. Pooled analysis of clinical studies included data from 14627 study participants aged 4 to 60 years (13839 children and 788 adults) who have been vaccinated with Qdenga. This included a reactogenicity subset of 3830 participants (3042 children and 788 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

Not known: cannot be estimated from the available data

Table 1: Adverse reactions from clinical studies (age 4 to 60 years) and post-authorization experience (age 4 years and older)

System Organ Class	Frequency	Adverse Reactions
Infections and infestations	Very common	Upper respiratory tract infection [a]
	Common	Nasopharyngitis Pharyngotonsillitis [b]
	Uncommon	Bronchitis Rhinitis
Immune system disorders	Not known	Anaphylactic reaction [c]
Metabolism and nutrition disorders	Very common	Decreased appetite [d]
Psychiatric disorders	Very common	Irritability [d]
Nervous system disorders	Very common	Headache Somnolence [d]
	Uncommon	Dizziness

System Organ Class	Frequency	Adverse Reactions
Gastrointestinal disorders	Uncommon	Diarrhoea Nausea Abdominal pain Vomiting
Skin and subcutaneous tissue disorders	Uncommon	Rash [e] Pruritus [f] 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 [f] Injection site pruritus [f] Influenza like illness
	Uncommon	Injection site haemorrhage [f] Fatigue [f] Injection site discolouration [f]

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] Adverse reaction observed post-authorization

[d] Collected in children below 6 years of age in clinical studies

[e] Includes rash, viral rash, rash maculopapular, rash pruritic

[f] Reported in adults in clinical trials

Paediatric population

Paediatric data in subjects 4 to 17 years of age

Pooled safety data from clinical trials are available for 13839 children (9210 aged 4 to 11 years and 4629 aged 12 to 17 years). This includes reactogenicity data collected in 3042 children (1865 aged 4 to 11 years and 1177 aged 12 to 17 years).

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 (11% versus 3%), upper respiratory tract infection (11% versus 3%), nasopharyngitis (6% versus 0.6%), pharyngotonsillitis (2% versus 0.3%), and influenza like illness (1% versus 0.1%). Adverse reactions reported less commonly in children than adults were injection site erythema (2% versus 27%), nausea (0.03% versus 0.8%) and arthralgia (0.03% versus 1 %).

The following reactions were collected in 357 children below 6 years of age vaccinated with Qdenga: decreased appetite (17%), somnolence (13%) and irritability (12%).

Paediatric data in subjects below 4 years of age, i.e. outside the age indication

Reactogenicity in subjects below 4 years of age was assessed in 78 subjects who received at least one dose of Qdenga of which 13 subjects received the indicated 2-dose regimen. Reactions reported with very common frequency were irritability (25%), fever (17%), injection site pain (17%) and loss of appetite (15%). Somnolence (8%) and injection site erythema (3%) were reported with common frequency. Injection site swelling was not observed in subjects below 4 years of age.

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 mean age of the per protocol 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 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) cases. Febrile episodes were confirmed by a validated, quantitative dengue RT-PCR to detect specific dengue serotypes.

2.1 Clinical efficacy data for 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)[a]

	Qdenga **N = 12,700[b]**	**Placebo** **N = 6316[b]**
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] The primary analysis of efficacy data were based on the Per Protocol Set, which consisted of all randomized subjects who did not have any major protocol deviations
[b] 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). 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 hospitalisation 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 to 7 days, haemorrhagic 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 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 years of age. The clinical efficacy of Qdenga in subjects from 17 years of age is based on bridging of immunogenicity data from clinical efficacy in subjects from 4-16 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 N = 20,067	**VE (95% CI) in preventing hospitalization due to VCD Fever N = 20,067**
Overall	61.2 (56.0, 65.8)	84.1 (77.8, 88.6)
By baseline dengue serostatus		
Seropositive	64.2 (58.4, 69.2)	85.9 (78.7, 90.7)
Seronegative	53.5 (41.6, 62.9)	79.3 (63.5, 88.2)

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

[a] The Safety Set consisted of all randomised subjects who received at least 1 dose of Qdenga or placebo

Additionally, VE in preventing DHF caused by any serotype was 70.0% (95% CI: 31.5%, 86.9%) and in preventing clinically severe VCD cases caused by any serotype was 70.2% (95% CI: -24.7%, 92.9%).

Up to four and a half 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.

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 (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 for subjects 4 to 16 years of age in endemic areas

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)[a]

	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

[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

* 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 for subjects 18 to 60 years of age in non-endemic areas

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 6**.

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

	Baseline Seropositive*		**Baseline Seronegative***	
	Pre-Vaccination N=68	1 month Post-Dose 2 Post-Vaccination N=67	Pre-Vaccination N=379	1 month Post-Dose 2 Post-Vaccination N=367
DENV-1				
GMT	13.9	365.1	5.0	268.1
95% CI	(9.5, 20.4)	(233.0, 572.1)	NE**	(226.3, 317.8)
DENV-2				
GMT	31.8	3098.0	5.0	2956.9

95% CI	(22.5, 44.8)	(2233.4, 4297.2)	NE**	(2635.9, 3316.9)
DENV-3				
GMT	7.4	185.7	5.0	128.9
95% CI	(5.7, 9.6)	(129.0, 267.1)	NE**	(112.4, 147.8)
DENV-4				
GMT	7.4	229.6	5.0	137.4
95% CI	(5.5, 9.9)	(150.0, 351.3)	NE**	(121.9, 155.0)

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) (Per Protocol Set for Immunogenicity)

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 of the GMT ratio of GMTs in 4-16 years old and GMTs in 18-60 years old is less than 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 (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 Shelf Life

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

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 or 10.

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 or 5.

- 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)

  Pack size of 1 or 5.

Not all pack sizes may be marketed.

6.6 Instructions for Use/Handling

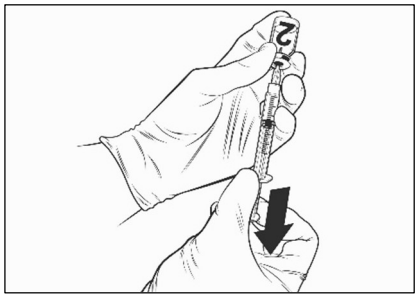
Instructions for reconstitution of the vaccine with the diluent (solvent) presented in vial

Qdenga is a 2-component vaccine that consists of a vial containing lyophilised vaccine and a vial containing diluent (solvent). The lyophilised 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.

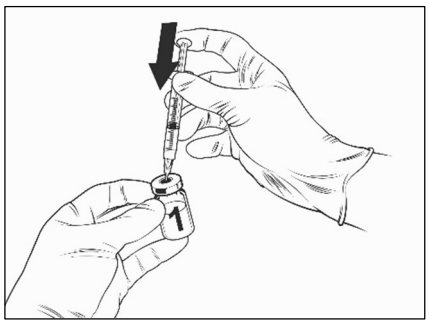
To reconstitute Qdenga, use only the diluent (0.22% sodium chloride solution) supplied with the vaccine since it is free of preservatives or other anti-viral substances. Contact with preservatives, antiseptics, detergents, and other anti-viral substances is to be avoided since they may inactivate the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

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



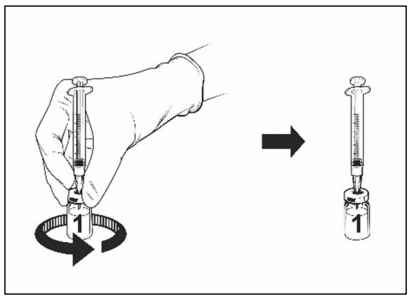
Diluent (solvent) vial

- 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 (solvent) 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.



Lyophilised vaccine vial

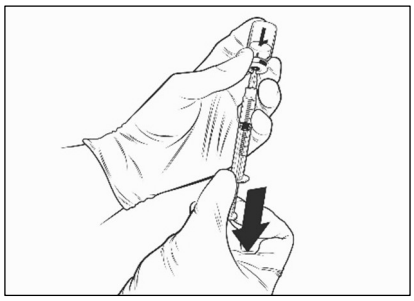
- Insert the needle of the syringe assembly into the lyophilised vaccine vial.
- Direct the flow of the diluent (solvent) toward the side of the vial while slowly depressing the plunger to reduce the chance of forming bubbles.



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, colourless to pale yellow, and essentially free of foreign particulates. Discard the vaccine if particulates are present and/or if it appears discoloured.



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 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.

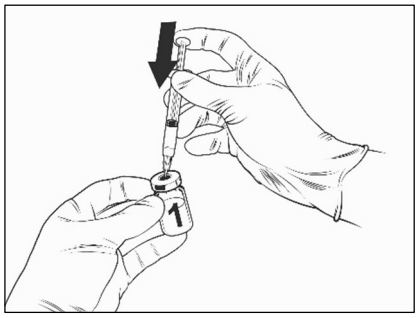
Instructions for reconstitution of the vaccine with diluent (solvent) presented in pre-filled syringe

Qdenga is a 2-component vaccine that consists of a vial containing lyophilised vaccine and diluent (solvent) provided in the pre-filled syringe. The lyophilised vaccine must be reconstituted with diluent prior to administration.

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

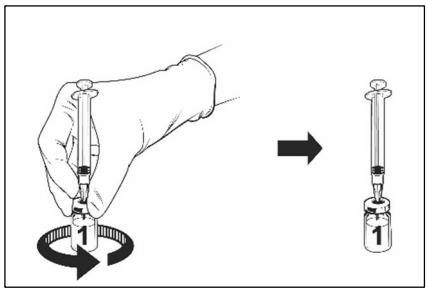
To reconstitute Qdenga, use only the diluent (0.22% sodium chloride solution) in the pre-filled syringe supplied with the vaccine since it is free of preservatives or other anti-viral substances. Contact with preservatives, antiseptics, detergents, and other anti-viral substances is to be avoided since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

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



Lyophilised vaccine vial

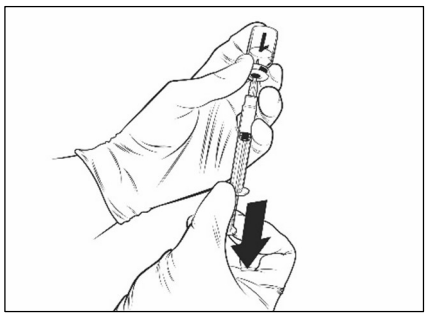
- Remove the cap from the vaccine vial and clean the surface of stopper on top of the vial using an alcohol wipe.
- Attach a sterile needle to the pre-filled syringe and insert the needle into the vaccine vial. The recommended needle is 23G.
- Direct the flow of the diluent (solvent) toward the side 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, colourless to pale yellow, and essentially free of foreign particulates. Discard the vaccine if particulates are present and/or if it appears discoloured.



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 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.

7. Marketing Authorization Holder

Takeda (Thailand), Ltd. Bangkok, Thailand

8. Marketing Authorization Number

2C 4/66 (NBC)

9. Date of Marketing Authorization

08 May 2023

10. Date of Revision of The Text

02 Jul 2024