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. This product contains genetically modified organisms (GMOs).
#Produced in Vero cells by recombinant DNA technology
**PFU = Plaque-forming units

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

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

The solvent is a clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Qdenga is indicated for the prevention of dengue disease in individuals from 4 years of age.

4.2 Posology and method of administration

Posology

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

Individuals from 4 years of age

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.

Other paediatric population (children <4 years of age)

The safety and efficacy of Qdenga in children aged less than 4 years has not yet been established.

Elderly

No dose adjustment is required in elderly individuals ≥60 years of age. See section 4.4.

Method of administration

After complete reconstitution of the lyophilised vaccine with the solvent, Qdenga should be administered by subcutaneous 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. 20 mg/day or 2 mg/kg body weight/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).
- Breast-feeding women (see section 4.6).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Anaphylaxis
Anaphylaxis has been reported in individuals who have received Qdenga. As with all injectable vaccines, appropriate medical treatment and supervision must 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 individual's 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). 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 sections 4.6 and 4.3).

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

Excipients

Qdenga contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Qdenga contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially 'potassium-free'.

4.5 Interaction with other medicinal products 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, in order to avoid neutralisation 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).

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 yellow fever seroprotection rate. 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 (HPV) vaccine (see section 5.1).

4.6 Fertility, 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 (see sections 4.4 and 4.3).

Pregnancy

Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

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-foetal development, parturition and post-natal development.

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

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).

Fertility

Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).
No specific studies have been performed on fertility in humans.

4.7 Effects on ability to drive and use machines

Qdenga has minor influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

In clinical studies, the most frequently reported reactions in subjects 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 viraemia

In clinical study DEN-205, transient vaccine viraemia 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 viraemia usually started in the second week after the first injection and had a mean duration of 4 days. Vaccine viraemia was associated with transient, mild to moderate symptoms, such as headache, arthralgia, myalgia and rash in some subjects. Vaccine viraemia was rarely detected after the second dose.
Dengue diagnostic tests may be positive during vaccine viraemia and cannot be used to distinguish vaccine viraemia from wild type dengue infection.

Tabulated list of adverse reactions

Adverse reactions associated with Qdenga obtained from clinical studies and post-authorisation experience are tabulated below (**Table 1**).

The safety profile presented below is based on data generated in placebo-controlled clinical studies and post-authorisation experience. Pooled analysis of clinical studies included data from 14,627 study participants aged 4 to 60 years (13,839 children and 788 adults) who have been vaccinated with Qdenga. This included a reactogenicity subset of 3,830 participants (3,042 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-authorisation experience (age 4 years and older)

MedDRA 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, including anaphylactic shock[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
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

MedDRA System Organ Class	Frequency	Adverse Reactions
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]

[a] Includes upper respiratory tract infection and viral upper respiratory tract infection
[b] Includes pharyngotonsillitis and tonsillitis
[c] Adverse reaction observed post-authorisation
[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 studies

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%).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

No cases of overdose have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Qdenga contains live attenuated dengue viruses. The primary mechanism of action of Qdenga is to replicate locally and elicit humoral and cellular immune responses against the four dengue virus serotypes.

Clinical efficacy

The clinical efficacy of Qdenga was assessed in study DEN-301, a pivotal Phase 3, double-blind, randomised, 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 randomised (2:1 ratio) to receive Qdenga or placebo, regardless of previous dengue infection.

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 maximise 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.

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**. 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 microneutralisation test (MNT_{50}) to allow Vaccine Efficacy (VE) assessment by baseline serostatus. The baseline dengue seronegativity rate for the overall per protocol population was 27.7%.

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 randomised subjects who did not have any major protocol violations, including not receiving both doses of the correct assignment of Qdenga or placebo
[b] Number of subjects evaluated

VE results according to the secondary endpoints, preventing hospitalisation 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 hospitalisation due to VCD fever, VCD fever by dengue serotype, VCD fever by baseline dengue serostatus, and 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 hospitalisations due to VCD fever[b], n (%)			
Hospitalisations due to VCD fever[c]	13 (0.1)	66 (1.0)	90.4 (82.6, 94.7)[d]
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 subjects	75 (0.8)	150 (3.3)	76.1 (68.5, 81.9)
VCD fever in baseline seronegative subjects	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)

VE: vaccine efficacy; 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] Most of the cases observed were due to DENV-2 (0 cases in Qdenga arm and 46 cases in Placebo arm)
[d] p-value <0.001

Early 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.

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 hospitalisation overall, by baseline dengue serostatus, and against individual serotypes by baseline serostatus from first dose to 54 months post second dose in study DEN-301 (Safety Set)

	Qdenga n/N	**Placebo n/N**	**VE (95% CI) in preventing VCD Fever[a]**	**Qdenga n/N**	**Placebo n/N**	**VE (95% CI) in preventing Hospitalisation due to VCD Fever[a]**
Overall	442/13380	547/6687	61.2 (56.0, 65.8)	46/13380	142/6687	84.1 (77.8, 88.6)
Baseline Seronegative, N=5,546						
Any serotype	147/3714	153/1832	53.5 (41.6, 62.9)	17/3714	41/1832	79.3 (63.5, 88.2)
DENV-1	89/3714	79/1832	45.4 (26.1, 59.7)	6/3714	14/1832	78.4 (43.9, 91.7)
DENV-2	14/3714	58/1832	88.1 (78.6, 93.3)	0/3714	23/1832	100 (88.5, 100)[b]
DENV-3	36/3714	16/1832	-15.5 (-108.2, 35.9)	11/3714	3/1832	-87.9 (-573.4, 47.6)
DENV-4	12/3714	3/1832	-105.6 (-628.7, 42.0)	0/3714	1/1832	NP[c]
Baseline Seropositive, N=14,517						
Any serotype	295/9663	394/4854	64.2 (58.4,69.2)	29/9663	101/4854	85.9 (78.7, 90.7)
DENV-1	133/9663	151/4854	56.1 (44.6, 65.2)	16/9663	24/4854	66.8 (37.4, 82.3)
DENV-2	54/9663	135/4854	80.4 (73.1, 85.7)	5/9663	59/4854	95.8 (89.6, 98.3)
DENV-3	96/9663	97/4854	52.3 (36.7, 64.0)	8/9663	15/4854	74.0 (38.6, 89.0)
DENV-4	12/9663	20/4854	70.6 (39.9, 85.6)	0/9663	3/4854	NP[c]

VE: vaccine efficacy, CI: confidence interval, VCD: virologically confirmed dengue, n: number of subjects, N: number of subjects evaluated, NP: not provided

[a] Exploratory analyses; the study was neither powered nor designed to demonstrate a difference between the vaccine and the placebo group

[b] Approximated using a one-sided 95% CI

[c] VE estimate not provided since fewer than 6 cases, for both TDV and placebo, were observed

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%).

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 (**Table 4**).

A year-by-year analysis until four and a half years after the second dose was conducted (**Table 5**).

Table 5: Vaccine efficacy in preventing VCD fever and hospitalisation overall and by baseline dengue serostatus in yearly intervals 30 days post second dose in study DEN-301 (Per Protocol Set)

		VE (95% CI) in preventing VCD Fever N[a] = 19,021	**VE (95% CI) in preventing Hospitalisation due to VCD Fever N[a] = 19,021**
Year 1[b]	Overall	80.2 (73.3, 85.3)	95.4 (88.4, 98.2)
	By baseline dengue serostatus		
	Seropositive	82.2 (74.5, 87.6)	94.4 (84.4, 98.0)
	Seronegative	74.9 (57.0, 85.4)	97.2 (79.1, 99.6)
Year 2[c]	Overall	56.2 (42.3, 66.8)	76.2 (50.8, 88.4)
	By baseline dengue serostatus		
	Seropositive	60.3 (44.7, 71.5)	85.2 (59.6, 94.6)
	Seronegative	45.3 (9.9, 66.8)	51.4 (-50.7, 84.3)
Year 3[d]	Overall	45.0 (32.9, 55.0)	70.8 (49.6, 83.0)
	By baseline dengue serostatus		
	Seropositive	48.7 (34.8, 59.6)	78.4 (57.1, 89.1)
	Seronegative	35.5 (7.4, 55.1)	45.0 (-42.6, 78.8)
Year 4[e]	Overall	62.8 (41.4, 76.4)	96.4 (72.2, 99.5)
	By baseline dengue serostatus		
	Seropositive	64.1 (37.4, 79.4)	94.0 (52.2, 99.3)
	Seronegative	60.2 (11.1, 82.1)	NP[f]

VE: vaccine efficacy, CI: confidence interval, VCD: virologically confirmed dengue, NP: not provided, N: total number of subjects in the per analysis set, [a] number of subjects evaluated in each year is different.
[b] Year 1 refers to 11 months starting 30 days after second dose.
[c] Year 2 refers to 13 to 24 months after second dose.
[d] Year 3 refers to 25 to 36 months after second dose.
[e] Year 4 refers to 37 to 48 months after second dose.
[f] VE estimate not provided since fewer than 6 cases, for both TDV and placebo, were observed.

Clinical efficacy for subjects from 17 years of age

No clinical efficacy study has been conducted in subjects from 17 years of age. The efficacy of Qdenga in subjects from 17 years of age is inferred from the clinical efficacy in 4 to 16 years of age by bridging of immunogenicity data (see below).

Immunogenicity

In the absence of correlates of protection for Dengue, the clinical relevance of immunogenicity data remains to be fully understood.

Immunogenicity data for subjects 4 to 16 years of age in endemic areas

The Geometric Mean Titres (GMTs) by baseline dengue serostatus in subjects 4 to 16 years of age in study DEN-301 are shown in **Table 6**.

Table 6: 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 Titre; 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

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 7**.

Table 7: GMTs of dengue neutralising antibodies in study DEN-304 (Per Protocol Set)

	Baseline Seropositive*		Baseline Seronegative*	
	Pre-Vaccination N=68	1 month Post-Dose 2 N=67	Pre-Vaccination N=379	1 month Post-Dose 2 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 Titre; 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 8)**. 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 8: GMT ratios between baseline dengue seronegative subjects in studies 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 Titre; CI: confidence interval; m: month(s)
*Non-inferiority: upper bound of the 95% CI less than 2.0.

Long-term persistence of antibodies

The long-term persistence of neutralising antibodies was shown in study DEN-301, with titres remaining well above the pre-vaccination levels for all four serotypes, up to 51 months after the first dose.

Co-administration with HPV

In study DEN-308 involving approximately 300 subjects aged 9 to 14 years who received Qdenga concomitantly with a 9-valent HPV vaccine, there was no effect on the immune response to the HPV vaccine. The study only tested co-administration of the first doses of Qdenga and the 9-valent HPV vaccine. Non-inferiority of the Qdenga immune response, when Qdenga and the 9-valent HPV vaccine were co-administered, has not been directly assessed in the study. In the dengue seronegative study population, dengue antibody responses after co-administration were in the same range as those observed in the Phase 3 study (DEN-301) where efficacy against VCD and hospitalised VCD was shown.

5.2 Pharmacokinetic properties

No pharmacokinetic studies have been performed with Qdenga.

5.3 Preclinical safety data

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 faeces 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.
Although no relevant hazard was identified, the relevance of the reproductive toxicity studies is limited, since rabbits are not permissive for dengue virus infection.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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 solvent provided.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

After reconstitution with the solvent provided, Qdenga should be used immediately.

If not used immediately, Qdenga must be used within 2 hours.

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.

From a microbiological point of view Qdenga should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C). Do not freeze.
Store in the original package.

For storage conditions after reconstitution of Qdenga, see section 6.3.

6.5 Nature and contents of container

Qdenga powder and solvent for solution for injection:

- Powder (1 dose) in glass vial (Type-I glass), with a stopper (butyl rubber) and aluminium seal with green flip-off plastic cap + 0.5 mL solvent (1 dose) in glass vial (Type-I glass), with a stopper (bromobutyl rubber) and aluminium seal with purple flip-off plastic cap

  Pack size of 1 or 10.

Qdenga powder and solvent for solution for injection in pre-filled syringe:

- Powder (1 dose) in vial (Type-I glass), with a stopper (butyl rubber) and aluminium seal with green flip-off plastic cap + 0.5 mL solvent (1 dose) 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 aluminium seal with green flip-off plastic cap + 0.5 mL solvent (1 dose) in pre-filled syringe (Type-I glass), with a plunger stopper (bromobutyl) and a tip cap (polypropylene), without needles

  Pack size of 1 or 5.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

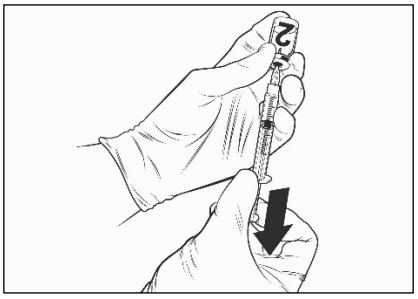
Instructions for reconstitution of the vaccine with the solvent presented in vial

Qdenga is a 2-component vaccine that consists of a vial containing lyophilised vaccine and a vial containing solvent. The lyophilised vaccine must be reconstituted with solvent 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.

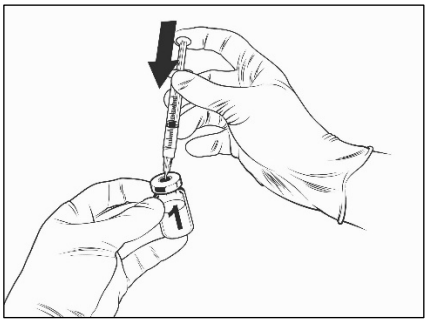
To reconstitute Qdenga, use only the solvent (0.22% sodium chloride solution) supplied with the vaccine since it is free of preservatives or other anti-viral substances. Contact with preservatives, antiseptics, detergents, and other anti-viral substances is to be avoided since they may inactivate the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

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



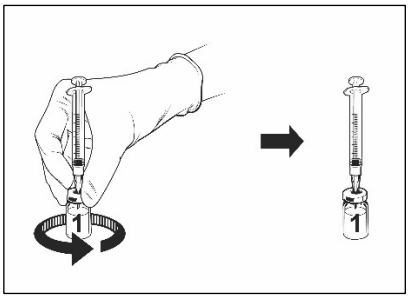
Solvent vial

- 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 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.
- Invert the syringe to bring the bubble back to the plunger.



Lyophilised vaccine vial

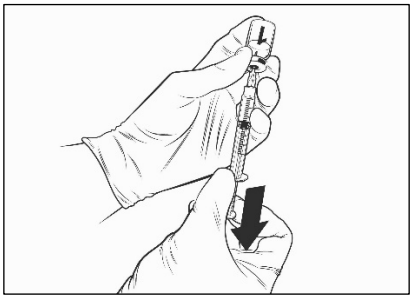
- Insert the needle of the syringe assembly into the lyophilised vaccine vial.
- Direct the flow of the solvent toward the side of the vial while slowly depressing the plunger to reduce the chance of forming bubbles.



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 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. From a microbiological point of view Qdenga should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

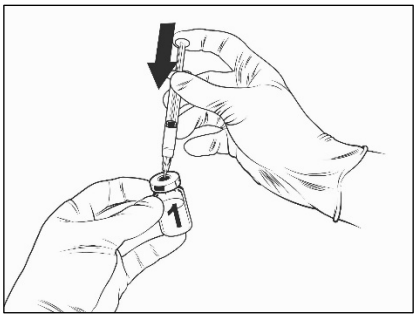
<u>Instructions for reconstitution of the vaccine with solvent presented in pre-filled syringe</u>

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

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

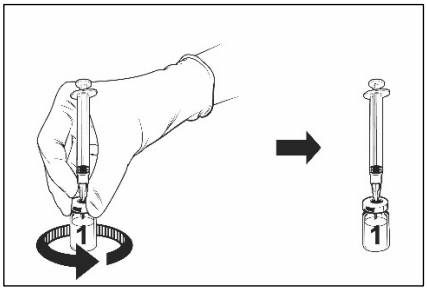
To reconstitute Qdenga, use only the solvent (0.22% sodium chloride solution) in the pre-filled syringe supplied with the vaccine since it is free of preservatives or other anti-viral substances. Contact with preservatives, antiseptics, detergents, and other anti-viral substances is to be avoided since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

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



Lyophilised vaccine vial

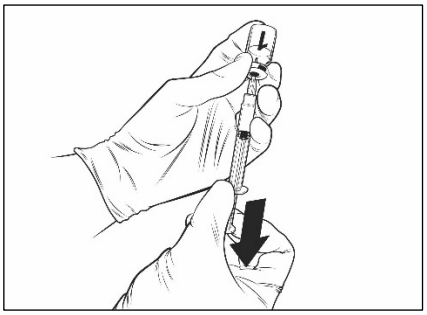
- Remove the cap from the vaccine vial and clean the surface of stopper on top of the vial using an alcohol wipe.
- Attach a sterile needle to the pre-filled syringe and insert the needle into the vaccine vial. The recommended needle is 23G.
- Direct the flow of the solvent toward the side of the vial 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 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. From a microbiological point of view Qdenga should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

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

7. MARKETING AUTHORISATION HOLDER AND IMPORTER

Takeda Israel Ltd.
25 Efal st.
P.O.B 4140
Petach Tikva 4951125
Israel

8. MARKETING AUTHORISATION NUMBER(S)

176-51-37674-00

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