▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION
QDENGA® DENGUE TETRAVALENT VACCINE (LIVE, ATTENUATED)

1. NAME OF THE MEDICINE

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 the full list of excipients, see section 6.1 LIST OF EXCIPIENTS

3. PHARMACEUTICAL FORM

Powder and solvent 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.

After reconstitution, the resulting solution should be clear, colourless to pale yellow, and essentially free of foreign particulates.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

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

The use of this vaccine should be in accordance with official recommendations.

4.2. DOSE AND METHOD OF ADMINISTRATION

Dosage

Individuals from 4 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

Paediatric 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and section 5.1 PHARMACODYNAMIC PROPERTIES but no recommendation on a posology can be made.

Impaired renal function
The safety and efficacy of QDENGA in this population has not been established.

Impaired hepatic function
The safety and efficacy of QDENGA in this population has not been established.

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 the 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.

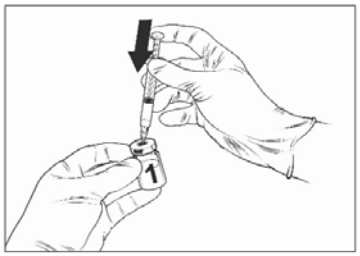
Instructions for use

QDENGA must be reconstituted 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.

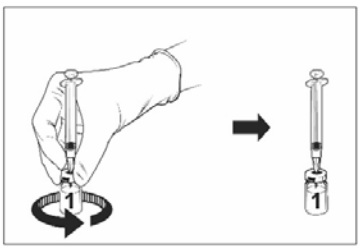
Reconstitution of the vaccine with solvent provided in a pre-filled syringe
QDENGA is a 2-component vaccine that consists of a vial containing lyophilised vaccine and solvent provided in the pre-filled syringe. The lyophilised vaccine must be reconstituted with solvent prior to administration.
Remove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



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.

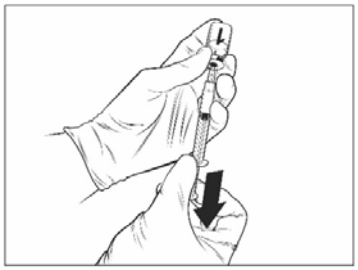
- Direct the flow of the solvent toward the side of the vial while slowly depressing the plunger to reduce the chance of forming bubbles.



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

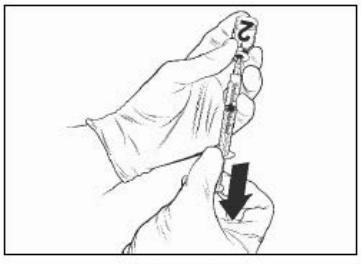
- Withdraw the entire volume of the reconstituted QDENGA solution with the same syringe until an air bubble appears in the syringe.
- Remove the needle syringe assembly from the vial. Hold the syringe with the needle pointing upwards, tap the side of the syringe to bring the air bubble to the top, discard 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 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.

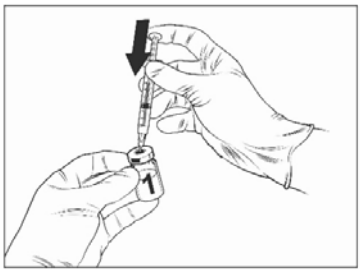
<u>Reconstitution of the vaccine with solvent provided in a vial</u>

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. Remove the vaccine and solvent vials from the refrigerator.

- Remove the caps from both vials and clean the surface of stoppers on top of the vials using an alcohol wipe.

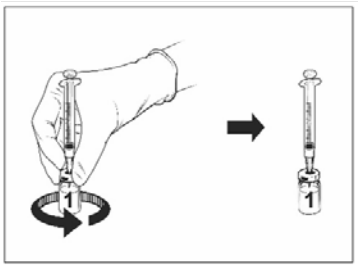

Solvent vial

- 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.
- Remove the needle syringe assembly from the solvent vial.
- Invert the syringe to bring the bubble back to the plunger.



Lyophilised vaccine vial

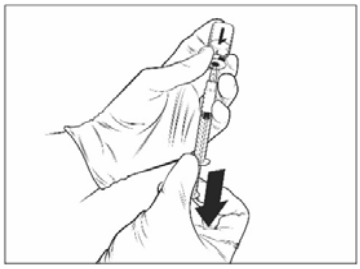
- Insert the needle of the syringe assembly into the lyophilised vaccine vial.
- Direct the flow of the solvent toward the side of the vial while slowly depressing the plunger to reduce the chance of forming bubbles.



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.

4.3. CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 LIST OF EXCIPIENTS, or hypersensitivity to a previous dose of QDENGA.
- Individuals with congenital or acquired immune deficiency, including those receiving immunosuppressive therapies such as 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, or any other medicinal product with known immunosuppressive properties including chemotherapy.
- Individuals with symptomatic HIV infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function.
- Pregnant women (see section 4.6 FERTILITY, PREGNANCY AND LACTATION).
- Breast-feeding women (see section 4.6 FERTILITY, PREGNANCY AND LACTATION).

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Anaphylaxis

Events of anaphylaxis have been reported during post-marketing experience (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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.

No clinical efficacy studies have been conducted in subjects above 17 years of age. Clinical efficacy of QDENGA in subjects above 17 years of age has been extrapolated from the bridging of immunogenicity data from clinical efficacy in subjects aged 4-16 years of age in the pivotal Phase 3 trial, DEN-301. No clinical studies evaluating the protective efficacy of QDENGA have been conducted in regions non-endemic for dengue.

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 FERTILITY, PREGNANCY AND LACTATION).

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.

Other

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

Use in hepatic impairment

The safety and efficacy of QDENGA in this population has not been established.

Use in renal impairment

The safety and efficacy of QDENGA in this population has not been established.

Use in the elderly

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

Paediatric use

See section 4.2 DOSE AND METHOD OF ADMINISTRATION, Paediatric patients.

Effects on laboratory tests

No studies have been performed on the interference of QDENGA with laboratory and/or diagnostic tests.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 neutralisation of the attenuated viruses contained in the vaccine.

QDENGA should not be administered to subjects receiving immunosuppressive therapies such as high doses of systemic corticosteroids within 4 weeks prior to vaccination, or any other medicinal product with known immunosuppressive properties including chemotherapy (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. 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. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No specific studies have been performed on fertility in humans.

Repeated exposure of female rabbits to a dose higher than the clinical dose of QDENGA by subcutaneous injection, 55, 35 and 14 days prior to mating showed no effects on female mating or fertility.

Use in pregnancy

Australian Pregnancy Categorisation: Category B2

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

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.

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.

Female New Zealand White (NZW) rabbits injected subcutaneously with a dose of QDENGA higher than the clinical dose, 55, 35 and 14 days before mating and on gestation days 7 and 28, showed no adverse effects on embryofetal or post-natal development. Neutralising antibodies against all vaccine serotypes were detected in all maternal rabbits and were detected in all fetuses and almost all pups following natural delivery.

Use in lactation

QDENGA is contraindicated during breast-feeding (see section 4.3 CONTRAINDICATIONS).

It is unknown whether QDENGA is excreted in human milk. A risk to the newborns/infants cannot be excluded.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) may temporarily have a minor influence on the ability to drive and use machines.

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

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 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, had a mean duration of 4 days, and was detected rarely after the second dose. Vaccine viraemia was associated with transient, mild to moderate symptoms, such as headache, arthralgia, myalgia and rash in some subjects that may also occur with dengue. Additional transient events observed post-authorisation were eye pain, thrombocytopenia and petechiae.

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 are tabulated below (Table 1).

The safety profile presented below is based on data generated in placebo-controlled clinical studies and post-marketing 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: ≥1/1000 to <1/100; rare: ≥1/10000 to <1/1000; very rare: <1/10000; 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)

System Organ Class	Frequency	Adverse Reactions
Infections and infestations	Very common	Upper respiratory tract infection[a]
	Common	Nasopharyngitis Pharyngotonsillitis[b]
	Uncommon	Bronchitis Rhinitis
Blood and lymphatic system disorders	Not known	Thrombocytopenia[c]
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
Eye disorders	Uncommon	Eye pain[c]
Gastrointestinal disorders	Uncommon	Diarrhoea Nausea Abdominal pain Vomiting

System Organ Class	Frequency	Adverse Reactions
Skin and subcutaneous tissue disorders	Uncommon	Rash[e] Pruritus[f] Urticaria
	Rare	Petechiae[c]
	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-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 trials

Paediatric population

Paediatric data in subjects 4 to 17 years of age

Pooled safety data from clinical trials are available for 13,839 children (9,210 aged 4 to 11 years and 4,629 aged 12 to 17 years). This includes reactogenicity data collected in 3,042 children (1,865 aged 4 to 11 years and 1,177 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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9. OVERDOSE

No cases of overdose have been reported.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 in Australia.

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 neutralising 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 non-structural protein 1 (NS1), and cell-mediated immune responses (CD4+, CD8+, and natural killer cells).

Clinical trials

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.

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 Neutralisation 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%.

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 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 = 6,316[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 was based on the Per Protocol Set, which consisted of all randomised subjects who did not have any major protocol deviations

[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 World Health Organisation (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 utilising 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, severe forms of dengue from 30 days to 18 months post second vaccination in study DEN-301 (Per Protocol Set)

	QDENDA N = 12,700[a]	Placebo N = 6,316[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)

	QDENDA N = 12,700[a]	Placebo N = 6,316[a]	VE (95% CI)
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; DENV: dengue virus serotype; DHF: dengue haemorrhagic fever; n: number of subjects;
VCD: virologically confirmed dengue; VE: vaccine efficacy

[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

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.

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 4.5 years post second dose in study DEN-301 (Safety Set)[a]

	QDENDA n/N	Placebo n/N	VE (95% CI) in preventing VCD Fever[a]	QDENDA n/N	Placebo n/N	VE (95% CI) in preventing hospitalisation due to VCD Fever[a]
Overall	442/13,380	547/6,687	61.2 (56.0, 65.8)	46/13,380	142/6,687	84.1 (77.8, 88.6)
Baseline Seronegative, N = 5,546						
Any serotype	147/3,714	153/1,832	53.5 (41.6, 62.9)	17/3,714	41/1,832	79.3 (63.5, 88.2)
DENV-1	89/3,714	79/1,832	45.4 (26.1, 59.7)	6/3,714	14/1,832	78.4 (43.9, 91.7)
DENV-2	14/3,714	58/1,832	88.1 (78.6, 93.3)	0/3,714	23/1,832	100 (88.5, 100)[b]
DENV-3	36/3,714	16/1,832	-15.5 (-108.2, 35.9)	11/3,714	3/1,832	-87.9 (-573.4, 47.6)
DENV-4	12/3,714	3/1,832	-105.6 (-628.7, 42.0)	0/3,714	1/1,832	NP[c]
Baseline Seropositive, N = 14,517						
Any serotype	295/9,663	394/4,854	64.2 (58.4, 69.2)	29/9,663	101/4,854	85.9 (78.7, 90.7)
DENV-1	133/9,663	151/4,854	56.1 (44.6, 65.2)	16/9,663	24/4,854	66.8 (37.4, 82.3)
DENV-2	54/9,663	135/4,854	80.4 (73.1, 85.7)	5/9,663	59/4,854	95.8 (89.6, 98.3)
DENV-3	96/9,663	97/4,854	52.3 (36.7, 64.0)	8/9,663	15/4,854	74.0 (38.6, 89.0)

DENV-4	12/9,663	20/4,854	70.6 (39.9, 85.6)	0/9,663	3/4,854	NP[c]

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

[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 Tetravalent Dengue Vaccine (Live, Attenuated) (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%).

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 (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 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 Seronegative	 82.2 (74.5, 87.6) 74.9 (57.0, 85.4)	 94.4 (84.4, 98.0) 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 Seronegative	 60.3 (44.7, 71.5) 45.3 (9.9, 66.8)	 85.2 (59.6, 94.6) 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 Seronegative	 48.7 (34.8, 59.6) 35.5 (7.4, 55.1)	 78.4 (57.1, 89.1) 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 Seronegative	 64.1 (37.4, 79.4) 60.2 (11.1, 82.1)	 94.0 (52.2, 99.3) NP[f]

CI: confidence interval; N: total number of subjects in the per analysis set; NP: not provided; VCD: virologically confirmed dengue; VE: vaccine efficacy

[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 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 below subsection on Immunogenicity).

Immunogenicity

During clinical development, immunogenicity data were collected in 9 studies with 3,877 subjects who received 2 doses of QDENGA 3 months apart; 2,796 of these subjects lived in dengue endemic areas and 1,081 subjects lived in non-endemic areas.

Neutralising antibody titres for each serotype were measured with MNT_{50} and presented as Geometric Mean Titres (GMTs).

In the tables below, the dengue serostatus at baseline (before the first injection) was identified as:

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

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 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 = 1,816*	1-month post-dose 2 N = 1,621	Pre-vaccination N = 702	1-month post-dose 2 N = 641
DENV-1				
GMT	411.3	2,115.2	5.0	184.2
95% CI	(366.0, 462.2)	(1,957.0, 2,286.3)	NE**	(168.6, 201.3)
DENV-2				
GMT	753.1	4,897.4	5.0	1,729.9
95% CI	(681.0, 832.8)	(4,645.8, 5,162.5)	NE**	(1,613.7, 1,854.6)
DENV-3				
GMT	357.7	1,761.0	5.0	228.0
95% CI	(321.3, 398.3)	(1,645.9, 1,884.1)	NE**	(211.6, 245.7)
DENV-4				
GMT	218.4	1,129.4	5.0	143.9
95% CI	(198.1, 240.8)	(1,066.3, 1,196.2)	NE**	(133.6, 155.1)

CI: confidence interval; DENV: dengue virus; GMT: Geometric Mean Titre; N: number of subjects evaluated; 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 = 1,815

** 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, randomised, 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 95% CI	13.9 (9.5, 20.4)	365.1 (233.0, 572.1)	5.0 NE**	268.1 (226.3, 317.8)
DENV-2 GMT 95% CI	31.8 (22.5, 44.8)	3,098.0 (2233.4, 4,297.2)	5.0 NE**	2,956.9 (2,635.9, 3,316.9)
DENV-3 GMT 95% CI	7.4 (5.7, 9.6)	185.7 (129.0, 267.1)	5.0 NE**	128.9 (112.4, 147.8)
DENV-4 GMT 95% CI	7.4 (5.5, 9.9)	229.6 (150.0, 351.3)	5.0 NE**	137.4 (121.9, 155.0)

CI: confidence interval; DENV: dengue virus; GMT: Geometric Mean Titre; N: number of subjects evaluated; 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 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
1-month post-dose 2	0.69 (0.58, 0.82)	0.59 (0.52, 0.66)	1.77 (1.53, 2.04)	1.05 (0.92, 1.20)
6-month post-dose 2	0.62 (0.51, 0.76)	0.66 (0.57, 0.76)	0.98 (0.84, 1.14)	1.01 (0.86, 1.18)

CI: confidence interval; DENV: dengue virus; GMT: Geometric Mean Titre.
*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.

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.

5.2 PHARMACOKINETIC PROPERTIES

No pharmacokinetic studies have been performed with QDENGA.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

QDENGA has not been evaluated for genotoxic potential.

Carcinogenicity

QDENGA has not been evaluated for carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Powder
Trehalose dihydrate
Poloxamer
Albumin
Monobasic potassium phosphate
Dibasic sodium phosphate dihydrate
Potassium chloride
Sodium 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

Unopened vial
In Australia, information on the shelf-life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

After reconstitution
After reconstitution with the 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 in a refrigerator at 2°C to 8°C. Do not freeze.

Store in the original packaging.

6.5 NATURE AND CONTENTS OF CONTAINER

QDENGA powder in vial and solvent in pre-filled syringe (with needles)

The powder for injection (1 dose) is filled in vial (Type 1 glass) closed with a rubber stopper and aluminium seal with green flip-off cap.

The solvent (0.5 mL) is filled in pre-filled syringe (Type 1 glass) closed with a rubber plunger stopper and a tip cap.

Each dose is provided with 2 separate needles (one 23G needle and one 25G needle).

Pack size of 1.

QDENGA powder in vial and solvent in vial

The powder for injection (1 dose) is filled in vial (Type 1 glass) closed with a rubber stopper and aluminium seal with green flip-off cap.

The solvent (0.5 mL) is filled in vial (Type 1 glass) closed with a rubber stopper and aluminium seal with purple flip-off cap.

Pack size of 1 or 10.

Not all presentations may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

QDENGA is for single use in one patient only. Discard any residue.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Not applicable

CAS number

Not applicable

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd

Level 39
225 George Street
Sydney NSW 2000
Australia

Telephone: 1800 012 612

www.takeda.com/en-au

9. DATE OF FIRST APPROVAL

8 April 2026

10. DATE OF REVISION

Not applicable

SUMMARY TABLE OF CHANGES

section changed	Summary of new information
N/A	