WHO PUBLIC ASSESSMENT REPORT (WHOPAR)

Qdenga Dengue Tetravalent Vaccine (Live, Attenuated)

Takeda GmbH, Germany

What is Qdenga?

Qdenga is a trade name for Takeda's Dengue Tetravalent Vaccine (Live, Attenuated) developed by recombinant DNA technology and produced in Vero cells by IDT Biologika GmbH, Germany, for Takeda GmbH. It consists of a molecularly characterized, attenuated dengue serotype 2 virus strain, and 3 recombinant dengue virus strains expressing surface antigens corresponding to dengue serotypes 1, 3 and 4. The genes of serotype-specific surface proteins engineered into dengue type 2 backbone. This product contains genetically modified organisms (GMOs).

Qdenga Dengue tetravalent vaccine (live attenuated) is a white to off-white lyophilized powder (compact cake) for injection. It is presented in a 2 mL USP and Ph.Eur Type I clear borosilicate glass vial, with a pharmaceutical grade rubber stopper, made out of bromobutyl rubber, and 13mm aluminium crimp cap with green flip-off seal. It is available in one dose vials co- packed with the diluent, in a pack size of ten doses per pack.

The Vaccine single-dose vial presentation consists of the following active components per 0.5mL dose:

Active components and quantity per dose	
Serotype TDV-1	≥ 3.3 log10 PFU/dose
Serotype TDV-2	≥ 2.7 log10 PFU/dose
Serotype TDV-3	≥4.0 log10 PFU/dose
Serotype TDV-4	≥4.5 log10 PFU/dose

The vaccine's excipients are: α,α-Trehalose dihydrate, Poloxamer 407, human serum albumin, potassium dihydrogen phosphate, disodium hydrogen phosphate, potassium chloride, sodium chloride, water for injections.

The stability data submitted by the manufacturer supports a shelf life of 18 months when the vaccine is stored between 2°C to 8°C. The vaccine should be shipped and stored at this recommended temperature, and it should not be frozen. The data also supports the use of a Vaccine Vial Monitor (VVM) Type 2 affixed on the flip-off seal cap for vaccines intended for supply to UN agencies.

The drug substance and drug product of Qdenga are manufactured at IDT Biologika GmbH, Am Pharmapark, 06861 Dessau-Rosslau. The batch release and manufacture of finished product are conducted at Takeda GmbH, Production site Singen, Robert-Bosch-Str. 8, 78224 Singen, Germany.

What is Qdenga used for?

Qdenga is indicated for the prevention of dengue disease in individuals from 6 years of age.

How is Qdenga used?

Qdenga which appears as a clear, colourless to pale yellow solution when reconstituted with the accompanying diluent, is administered as a single dose 0.5mL injection subcutaneously, preferably in the upper arm in the region of the deltoid. Qdenga should not be administered by intramuscular injection and it must be used within 2 hours from reconstitution when maintained at room temperature (Up to 32.5°C)

What are the vaccine characteristics?

Qdenga must be stored as recommended by the manufacturer, between 2°C to 8°C. Under these recommended storage conditions, the vaccine is stable for 18 months from the date of manufacture.

The vaccine does not contain preservative.

Cold chain volume per dose of 16.09 cm^3 (in secondary packaging).

Who is the regulatory authority responsible for its oversight vis a vis WHO?

The European Medicines Agency (EMA) is the Regulatory Authority of record for the WHO prequalification procedure. The EMA EU-M4all and EU MAA CHMP Positive Opinions was issued for Takeda's Dengue tetravalent vaccine (TDV) on 13 October 2022.

How has Qdenga been studied from the clinical point of view?

This prequalification application followed a streamlined procedure with review of the assessment report of the reference National Regulatory Authority, some text of which is reproduced below.

A total of 19 trials (8 phase 3 trials, 6 phase 2 trials, and 5 phase 1 trials) with more than 28,000 subjects Monitoring of febrile illness and severe forms of dengue (according to predefined criteria) was performed in the pivotal Trial, in which a total of 20,071 subjects received at least 1 dose of trial vaccine. The trial is ongoing. Results based on efficacy, immunogenicity, and safety data up to 54 months post second vaccine dose are summarized in detail for this submission. Monitoring of febrile illness and severe dengue was also performed in two phase 2 Trials (data up to 36 months post second dose was available in one study and data up to 48 months after first dose in the other), but without a predefined dengue severity assessment.

Long-term safety data are available for up to 54 months (4.5 years) after the second dose from the pivotal phase 3 Trial, up to 48 months (4 years) after the first dose from one phase 2 Trial, and up to 36 months (3 years) post second dose from another phase 2 Trial.

Additionally, booster dose evaluations have started in 2 trials (within dengue-endemic and non-endemic areas) with final data becoming available at a later date (preliminary safety data up to the overall safety data cut-off date included in this submission).

Immunogenicity and safety data after co-administration of TDV with either YF vaccine or hepatitis A virus (HAV) vaccine have been evaluated in the completed phase 3 Trials. Results were provided. In addition, preliminary safety data after co-administration of TDV with a 9-valent human papillomavirus (9vHPV) vaccine are available from ongoing phase 3 Trial. Efficacy and/or safety data based on interim or final CSRs are available for 17 trials.

The primary VE objective for the pivotal trial was met, with overall VE of 80.2% in preventing virologically confirmed dengue (VCD) by any serotype from 30 days post-second vaccination to 12 months post dose 2. The secondary objectives were also met. At 18 months post dose 2, TDV vaccination resulted in 90.4% reduction in hospitalized dengue (key secondary endpoint) and 73.3% reduction in VCD in the active arm. When stratified by baseline serostatus, VCD for those seropositive at baseline was 76.1% and for those seronegative at baseline was 66.2%. This difference, however, was not significant given the overlapping 95% confidence intervals of the point estimates.

Reduction of VCD cases was observed for DENV-1, DENV-2 and DENV-3 infections, with efficacy ranging from 48.9% (DENV-3) to 95.1% (DENV-2) from 30 days post second vaccination to 18 months post dose 2. VE for DENV-4 VCD was inconclusive owing to the small number of cases.

The evaluation of unsolicited AEs, AEs leading to vaccine and/or trial discontinuation, MAAEs, and SAEs revealed no important safety risks. The long-term SAE follow-up (up to 54 months from main study did not reveal any important safety risk, irrespective of age group or baseline serostatus.

The totality of data on VCD, hospitalized VCD, and severe forms of dengue, along with the clinical characteristics of these cases, as assessed in the trials did not reveal an identified risk of increased disease severity or disease enhancement attributable to vaccination in the post-vaccination follow-up period. There was insufficient evidence for increased disease severity and/or risk of hospitalization for VCD caused by DENV-3 or DENV-4 in baseline seronegative subjects, and data did not suggest an increase in severity over time.

Co-administration of TDV with YF or HAV vaccines was generally well tolerated and had no negative effect on the safety and reactogenicity of either vaccine. YF vaccine immunogenicity was not affected when administered concomitantly with TDV. However, dengue antibody responses were decreased to some extent following concomitant administration of TDV with the YF vaccine compared with separately administered vaccines, with non-inferiority shown for DENV-2, DENV-3, and DENV-4, but not for DENV-1.

Other information about evaluation of Qdenga

Evaluation of Qdenga application was supported by the evaluation reports provided by the European Medicines Agency (EMA). This included the final assessment reports conducted by the Agency and the positive opinion of the CHMP on granting the marketing authorization of the vaccine.

The vaccine prequalification dossier was submitted in a CTD format. The vaccine meets WHO Technical Report Series (e.g., Technical Report Series No. 979 Annex 2; Guidelines on the quality, safety and efficacy of dengue tetravalent vaccines (live, attenuated). In addition, the vaccine was found in compliance with WHO programmatic suitability criteria and UN specific labelling requirement.

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