POLICY DETERMINATION

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

***Current Policy Effective Date: 9/1/25**
(See policy history boxes for previous effective dates)

Title: Dengue vaccine, quadrivalent, live, 2 dose schedule, for subcutaneous use

Brief Description of Service:

Dengue is a mosquito-borne viral disease that spreads rapidly around the globe and is considered 1 of the WHO's (2019) top 10 threats to global health. Dengue is a leading cause of fever among travelers to Latin America, the Caribbean and Southeast Asia. Dengue is caused by one of the 4 dengue virus serotypes. Initial infection with dengue typically results in either no symptoms or a mild illness that can be mistaken for the flu or another viral infection. Lifelong immunity is achieved once an individual recovers from a specific serotype, but only for that serotype. Infection from any of the remaining serotypes is associated with an increased risk of severe disease or possibly death. Dengue has appeared in more than 125 countries and is 1 of the primary causes of hospitalization in children in many parts of the world.

In an ongoing phase III randomized, double-blind, placebo-controlled clinical trial, the efficacy, safety and immunogenicity of Takeda's tetravalent dengue vaccine (TDV) is being investigated in 20,099 healthy children aged 4-16 years old. Prior studies of Qdenga have indicated an 80% efficacy at preventing symptomatic infection at 12 months and a 90% efficacy at preventing hospitalizations at 18 months. The 2-shot series showed the ability to provide protection for 4.5 years.

The TDV vaccine (Qdenga; TAK-003) consists of a live attenuated dengue serotype 2 (DENV-2) virus component and 3 chimeric virus components constructed by incorporating the DENV-1, -3, and -4 protein genes into the recombinant DENV-2 vaccine, thus providing a genetic backbone for all 4 virus subtypes.

The primary outcome measure includes vaccine efficacy (VE) of 2 doses of tetravalent dengue vaccine candidate (TDV) in preventing virologically confirmed dengue fever induced by any dengue serotype. Other outcome measures include:

- VE of 2 doses of TDV in preventing virologically confirmed dengue fever induced by each dengue serotype and/or any dengue serotype in participants dengue seronegative or seropositive at baseline
- VE of 2 doses of TDV in preventing hospitalization due to virologically confirmed dengue fever or severe dengue fever induced by any dengue serotype
- Percentage of participants with solicited local injection site and/or systemic adverse events by severity in the safety subset
- Severity of solicited systemic adverse events in the safety subset
- Percentage of participants with any unsolicited and/or serious adverse events in the safety subset
- Percentage of participants with fatal serious adverse events and serious adverse events related to study drug during the first and second half of part 3
- Percentage of participants with a seropositive response for each of the 4 or with multiple dengue serotypes in the immunogenicity subset
- Geometric Mean Titers (GMTs) of Neutralizing Antibodies for Each of the Four Dengue Serotypes in the Immunogenicity Subset

The FDA granted a priority review designation for a biologics license application (November 2022) of Qdenga (TAK-003) for the prevention of dengue disease caused by any dengue virus serotype in individuals 4-60 years of age.

Takeda voluntarily withdrew its application for Qdenga (TAK-003) before the FDA in July 2023, citing the FDA's requirement for additional data not captured in the phase III studies. Qdenga is a dengue vaccine based on a live-attenuated dengue serotype 2 virus that provides the genetic “backbone” for all 4 dengue virus serotypes

At the present time, Takeda’s Dengue Vaccine Candidate, represented by procedure code 90584 has not received approval from the U.S. Food and Drug Administration and it is not recommended by the Advisory Committee on Immunization Practices.

Recommendation:

Dengue vaccine, quadrivalent, live, 2-dose schedule, for subcutaneous use is experimental/investigational. The U.S. Food and Drug Administration (FDA) has not approved this vaccine and it is not currently recommended by the Advisory Committee on Immunization Practices.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

90584

References:

1. Chen, W. "Updates on Dengue Vaccines." *Centers for Disease Control and Prevention.* 2024. https://stacks.cdc.gov/view/cdc/134675 Accessed June 11, 2025.
2. George, S. L. et al. Safety and Immunogenicity of a live attenuated tetravalent dengue vaccine candidate in flavivirus-naive adults: a randomized, double blinded phase 1 clinical trial. J. Infect. Dis. 212, 1032–1041 (2015).
3. LakKumar, F. Potential Impact of Takeda's Dengue Vaccine Candidate Reinforced by Long-Term Safety and Efficacy Results. *Takeda*. (2021) https://www.takeda.com/newsroom/newsreleases/2021/potential-impact-of-takedas-dengue-vaccine-candidate-reinforced-by--long-term-safety-and-efficacy-results/. Accessed June 11, 2025.
4. Osorio, J. E., et al. Development of a recombinant, chimeric tetravalent dengue vaccine candidate. Vaccine 33, 7112–7120 (2015).
5. Rupp, R. et al. Safety and immunogenicity of different doses and schedules of a live attenuated tetravalent dengue vaccine in healthy adults: a phase 1b randomized study. Vaccine 33, 6351–6359 (2015).
6. Sirivichayakul, C. et al. Safety and Immunogenicity of a tetravalent dengue vaccine candidate in healthy children and adults in dengue-endemic regions: a randomized, placebo-controlled phase 2 study. J. Infect. Dis. 213, 1562–1572 (2016).
7. Takeda. "Takeda's Biologics License Application (BLA) for Dengue Vaccine Candidate (TAK-003) Granted Priority Review by U.S. Food and Drug Administration." November 2022. https://www.takeda.com/newsroom/newsreleases/2022/takedas-biologics-license-application-bla-for-dengue-vaccine-candidate-tak-003-granted-priority-review-by-us-food-and-drug-administration. Accessed June 11, 2025.
8. U.S. National Library of Medicine. Efficacy, Safety and Immunogenicity of Takeda's Tetravalent Dengue Vaccine (TDV) in Healthy Children (TIDES). NCT02747927. https://clinicaltrials.gov/ct2/show/NCT02747927?term=TIDES&draw=2&rank=7. Accessed June 11, 2025.
9. World Health Organization. Factsheet. Dengue and Severe Dengue. April 23, 2024. https://www.who.int/en/news-room/fact-sheets/detail/dengue-and-severe-dengue. Accessed June 11, 2025.

10. World Health Organization. Ten threats to global health in 2019. https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019. Accessed June 11, 2025.

Joint Blue Cross/BCN Medical Policy History

Policy Effective Date	Blue Cross Signature Date	BCN Signature Date	Comments
9/1/22	6/21/22		• Policy determination – EI
9/1/23	6/13/23		• Routine maintenance (slp) • Vendor Managed: N/A
9/1/24	6/11/24		• Routine maintenance (slp) • Vendor Managed: N/A
9/1/25	6/17/25		• Routine maintenance (ls) • Vendor Managed: N/A

Next Review Date: 2nd Qtr, 2026