Approval Date: January 22, 2020

Product: DENGVAXIA

Proper Name: Dengue Tetravalent Vaccine, Live

Manufacturer: Sanofi Pasteur Inc

Indication:

DENGVAXIA® (Dengue Tetravalent Vaccine, Live) is a vaccine indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3, and 4. DENGVAXIA is approved for use in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.

Description: DENGVAXIA (Dengue Tetravalent Vaccine, Live) is a sterile suspension for subcutaneous injection.

BLA: 125682

Regulatory Milestone: No data available

PDUFA Goal Date: May 1, 2019

Package Insert: Package Insert - Dengvaxia

Summary Basis for Regulatory Approval: Summary Basis for Regulatory Action - Dengvaxia

European Public Assessment Report: Human medicine European public assessment report (EPAR): Dengvaxia

Advisory Committee:

A Vaccines and Related Biological Products Committee (VRBPAC) meeting was convened on March 7, 2019. The committee discussed the safety and efficacy data derived from the clinical disease endpoint efficacy studies conducted in subjects 2 – 16 years of age in the Asian Pacific Region and South America, including Puerto Rico. The committee noted that data support the efficacy of DENGVAXIA in pediatric subjects with confirmed prior dengue infection and living in endemic areas. The committee expressed concern about the safety signal identified in the efficacy studies, namely an increased risk of hospitalization and severe dengue in individuals with no prior exposure to dengue who were vaccinated with DENGVAXIA and subsequently infected with dengue. There was consensus that the dengue infection status of individuals would need to be determined prior to vaccination if the vaccine was licensed and recommended for use. The committee expressed concern that currently available serological tests may lead to false positive results because of cross-reactivity with other flaviviruses. The committee also noted the operational/logistical and infrastructure concerns of serotesting prior to vaccination. There was broad recognition of the value of an FDA cleared rapid diagnostic assay to establish prior exposure to dengue in individuals to be vaccinated.

The committee expressed concern about inferring vaccine effectiveness in adults 18 to 45 years of age based on the pediatric efficacy studies and antibody titers in adults because available immunogenicity data in adults were derived from small studies and conducted in countries with high dengue endemicity, i.e., Vietnam and India. The committee was concerned that these data may not reflect immune responses in adults living in Puerto Rico. The committee opined that in the absence of immunogenicity data more relevant to adults living in Puerto Rico, it was difficult to infer effectiveness in the adult population.

The committee's concerns were discussed between Sanofi Pasteur and CBER after the March 7, 2019, VRPBAC meeting. Both CBER and Sanofi Pasteur agreed that additional studies relevant to the adult population in Puerto Rico would address the committee's concerns and could support inclusion of individuals 17 through 45 years of age in the indication. Sanofi Pasteur informed CBER that they decided for this BLA submission to pursue an indication only for individuals 9 through 16 years of age and requested a revised indication that does not include individuals 17 through 45 years of age.

NCT Numbers:

- NCT04170140
- NCT04486638
- NCT03803618
- NCT00842530
- NCT03960385
- NCT00993447
- NCT03465254
- NCT02979535
- NCT02948933
- NCT04023708
- NCT02993757
- NCT02992418

EudraCT Numbers:

- 2019-000994-22
- 2019-003135-36
- 2020-002854-25
- 2019-000993-44
- 2019-003136-23

Publications:

- Coronel, D., García-Rivera, E. J., Rivera, M., Arredondo-García, J. L., Dietze, R., Perroud, A. P., Cortés, M., Bonaparte, M., Zhao, J., Tila, M., Jackson, N., Zambrano, B., & Noriega, F. (2019). Dengue Vaccine Booster in Healthy Adolescents and Adults in Latin America: Evaluation 4-5 Years After a Primary 3-Dose Schedule. *The Pediatric infectious disease journal*, *38*(5), e90–e95. https://doi.org/10.1097/INF.0000000000002286
- Carpp, L. N., Fong, Y., Bonaparte, M., Moodie, Z., Juraska, M., Huang, Y., Price, B., Zhuang, Y., Shao, J., Zheng, L., Chambonneau, L., Small, R., Sridhar, S., DiazGranados, C. A., & Gilbert, P. B. (2020). Microneutralization assay titer correlates analysis in two phase 3

trials of the CYD-TDV tetravalent dengue vaccine in Asia and Latin America. *PloS one*, *15*(6), e0234236. https://doi.org/10.1371/journal.pone.0234236

- Lin, L., Lyke, K. E., Koren, M., Jarman, R. G., Eckels, K. H., Lepine, E., McArthur, M. A., Currier, J. R., Friberg, H., Moris, P., Keiser, P. B., De La Barrera, R., Vaughn, D. W., Paris, R. M., Thomas, S. J., & Schmidt, A. C. (2020). Safety and Immunogenicity of an $AS03_B$-Adjuvanted Inactivated Tetravalent Dengue Virus Vaccine Administered on Varying Schedules to Healthy U.S. Adults: A Phase 1/2 Randomized Study. *The American journal of tropical medicine and hygiene*, *103*(1), 132–141. https://doi.org/10.4269/ajtmh.19-0738
- Plennevaux, E., Moureau, A., Arredondo-García, J. L., Villar, L., Pitisuttithum, P., Tran, N. H., Bonaparte, M., Chansinghakul, D., Coronel, D. L., L'Azou, M., Ochiai, R. L., Toh, M. L., Noriega, F., & Bouckenooghe, A. (2018). Impact of Dengue Vaccination on Serological Diagnosis: Insights From Phase III Dengue Vaccine Efficacy Trials. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, *66*(8), 1164–1172. https://doi.org/10.1093/cid/cix966
- Glass, A., Polhemus, M., Wang, D., Jarman, R. G., Thomas, S. J., Friberg, H., Currier, J. R., Bonaparte, M., De La Barra, R., Princiotta, M. F., Abbott, M., Cuzzo, B., Machabert, T., Sridhar, S., & Endy, T. P. (2020). The Effects of Japanese Encephalitis Vaccine and Accelerated Dosing Scheduling on the Immunogenicity of the Chimeric Yellow Fever Derived Tetravalent Dengue Vaccine: A Phase II, Randomized, Open-Label, Single-Center Trial in Adults Aged 18 to 45 Years in the United States. *The Journal of infectious diseases*, *221*(7), 1057–1069. https://doi.org/10.1093/infdis/jiz592