Physician Educational Material Dengvaxia™

This Physician Educational Material provides practical guidance on the use of Dengvaxia in Singapore. For full details, please refer to the Singapore package insert.

- **Approved Indication**

  Dengvaxia is indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 12 through 45 years of age with test-confirmed previous dengue infection.

- **Posology and method of administration**

  Screening

  Dengvaxia should only be administered to individuals with a previous dengue infection. Previous dengue infection must be confirmed by a test, either documented in the medical history or performed prior to vaccination.

  In non-endemic areas or low transmission settings, the lower the proportion of true seropositive individuals, the higher the risk of false seropositives with any test used to determine dengue serostatus. Thus, testing performed prior to vaccination should be limited to individuals who have been in potential contact with dengue virus (e.g. individuals who lived before or had recurrent stay in endemic areas) and who are likely to be exposed to dengue in the future. The objective is to minimize the risk of a false positive test, as in non-endemic areas, the proportion of individuals truly infected by dengue is considered generally very low.

  Posology

  The vaccination schedule consists of 3 subcutaneous injections of 0.5 mL to be administered at 6-month intervals. The recommended injection site is the deltoid region.

  Dengvaxia should not be administered to individuals less than 12 years of age.

  Vaccination is not recommended for individuals who have not been previously infected by dengue virus.

  For individuals with unknown history of prior dengue exposure, previous infection can be substantiated through serotesting.

  Booster dose

  Current data suggest that a booster after primary vaccination with Dengvaxia does not provide any additional benefit.

- **Considerations for the Singaporean population:**

  Clinical efficacy studies conducted in the 12 to 16 years-old population in endemic countries showed that the vaccine efficacy against symptomatic virologically confirmed dengue (VCD) cases due to any serotype is 69.2% and 60.4%, 53.2%, 76.2% and 88.0% for serotypes 1, 2, 3 and 4 respectively.

  The vaccine efficacy against severe VCD cases and against hospitalized VCD cases (i.e., hospital admission due to dengue, regardless of severity) is 95.5% (95% CI: 64.8; 99.4) and 81.3% (95% CI: 63.8; 90.4) respectively.

  Vaccine efficacy against VCD was demonstrated in dengue immune[1] subjects at baseline (81.9%) and also dengue non-immune[1] subjects at baseline (52.5%). This vaccine efficacy was measured over the 25-month period after the first dose and using PRNT 50 test in a subset of subjects aged 9 to 16 years.

  No clinical efficacy studies were conducted in Singapore. For the Singapore population, a safety and clinical immunogenicity study (CYD28) was conducted in subjects aged 2 to 45 years old. In the CYD28 study overall, an immune response to the vaccine was observed in all age groups, with an increase in antibody levels (presented as geometric mean titers [GMTs]) for each serotype 28 days after the third dose of vaccine. Post-dose 3 GMTs were lower than in the other studies conducted in highly endemic countries and low GMTs were observed in dengue non-immune subjects at baseline. Post-dose 3 GMTs were also low in the out-of indication 2- to 5-year-old subjects included in the CYD14 Phase III study, for which the cumulative relative risk of hospitalized dengue illness was 2.108 (95% CI: 1.14; 4.21) within the 3 years of long-term follow-up that includes both hospital phase and partial surveillance expansion phase data (from 1 to 4 years after the third dose) and 1.360 (95% CI: 0.86; 2.22) within the first five years after the first dose.

  In an exploratory analysis of up to 6 years of follow up from the first dose in three efficacy studies, an increased risk of hospitalization for dengue including clinically severe dengue (predominantly Dengue Hemorrhagic Fever grade 1 or 2 [WHO 1997]) has been observed in vaccinees with no previous dengue infection.

  In Singapore, for individuals with unknown history of prior dengue exposure, serostatus testing if available may provide some additional information to inform the benefit/risk considerations following vaccination with Dengvaxia in these individuals.

- **Special warnings and precautions for use**

  - As with any vaccine, Dengvaxia does not offer 100% protection against the dengue virus. Personal protection measures against mosquito bites are still recommended after vaccination.

[1] The terms “immune and non-immune” are used to describe the presence or not of antibodies at baseline. Immune is not used to imply that subjects are protected from dengue infection.

- Healthcare professionals should follow-up and appropriately manage any vaccinated individuals with signs and symptoms of dengue fever, with particular attention to dengue warning signs (e.g., high fever, severe abdominal pain or tenderness, persistent vomiting, mucosal bleeding, somnolence and hyperactivity according to WHO guidelines 2009).
- Individuals who have not been previously infected by the dengue virus should not be vaccinated because an increased risk of hospitalization for dengue and clinically severe dengue (predominantly grade 1 or 2 Dengue Hemorrhagic Fever [WHO 1997]) has been observed in not previously infected, vaccinated individuals during the long-term follow up of clinical trials.
- In the absence of documented prior dengue virus infection, previous infection must be confirmed by a test before vaccination. To avoid vaccination of false positives, only test methods with adequate performance in terms of specificity and cross-reactivity based on the local disease epidemiology should be used.
- Before administering any biological, the person responsible for administration must take all precautions to prevent allergic or other reactions. As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in the event of an anaphylactic reaction following the administration of Dengvaxia.
- Adrenaline (1:1000) and other appropriate agents used to control immediate allergic reactions must be available to treat unexpected events such as anaphylaxis.
- Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to injection with a needle. Procedures should be in place to prevent injury from falling and to manage syncopal reactions.

- **Contra-Indications:**

  Dengvaxia must not be administered to individuals:
  - with a history of severe allergic reaction to any component of Dengvaxia or after prior administration of Dengvaxia or a vaccine containing the same components.
  - with congenital or acquired immune deficiency that impairs cell-mediated immunity, including immunosuppressive therapies such as chemotherapy or high doses of systemic corticosteroids generally given for 2 weeks or more.
  - with symptomatic HIV infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function.
  - pregnant women, or breastfeeding women.

  Administration of Dengvaxia must be postponed in individuals suffering from moderate to severe febrile or acute disease.

- **Adverse reactions (ARs) from clinical studies**

  ARs within 28 days after any dose of Dengvaxia in subjects 9 through 60 years of age are presented below, based on safety data collected from clinical studies.

  ARs that are **very commonly** (≥10%) reported include: headache, myalgia, malaise, injection site pain, asthenia and fever.These ARs were of mild to moderate severity and of short duration (0 to 3 days). Onset was typically observed 0 to 3 days after the injection, except for fever which appeared within 14 days after the injection.

  ARs that are **commonly** (≥1% and <10%) reported include: injection site reactions (erythema,

haematoma, swelling, pruritus).

ARs that are **uncommonly** (≥0.1% and <1%) reported include: upper respiratory tract infection, lymphadenopathy, dizziness, migraine, oropharyngeal pain, cough, rhinorrhoea, nausea, rash, urticaria, neck pain, arthralgia, injection site induration, influenza-like illness.

ARs that are very rarely (<0.01%) reported include: allergic including anaphylactic reactions.

In phase III efficacy studies (CYD14 and CYD15), isolated neurological disorder related serious adverse events have been observed in subjects 8 through 11 years of age: acute polyneuropathy in one subject of 10 years of age, convulsion (reported as "seizures not specified") in one subject of 11 years of age, and acute disseminated encephalomyelitis (ADEM) in one subject aged 8 years of age. These events were isolated and therefore not listed in the list of ARs above.

- **Call for adverse event reporting:**

Medical practitioners are encouraged to report any adverse events suspected to be associated with Dengvaxia to Sanofi by emailing to PV.SIN@Sanofi.com or by calling +65-6226 3836. Adverse events could also be reported to the Vigilance and Compliance Branch, HSA by emailing to HSA_productsafety@hsa.gov.sg or report online at https://www.hsa.gov.sg/adverse-events.

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