# Fact Sheet for Healthcare Providers
# Interpreting ADVIA Centaur® Zika Test Results

**September 18, 2017**

**Dear Healthcare Provider:**

The United States (U.S.) Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to authorize the use of the Siemens Healthcare Diagnostics Inc. (Siemens) ADVIA Centaur® Zika test. This assay provides *in vitro* qualitative detection of IgM antibodies to the Zika virus. The ADVIA Centaur Zika test is intended for use in human serum and plasma (potassium EDTA or lithium heparin, each collected alongside a patient-matched serum specimen) specimens of individuals meeting Centers for Disease Control and Prevention (CDC) Zika clinical and/or epidemiological criteria for testing (see www.cdc.gov/zika/hc-providers/index.html) by laboratories in the U.S. that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, to perform high or moderate complexity tests, or by similarly qualified non-US laboratories. Specimens used with the ADVIA Centaur Zika test should not be collected prior to 8 days after onset of symptoms or risk of exposure. This test should be performed according to CDC's algorithm for Zika testing (see https://www.cdc.gov/zika/laboratories/lab-guidance.html).

The information in this Fact Sheet is to inform you of the significant known and potential risks and benefits of the emergency use of the ADVIA Centaur Zika test http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm).

## Why is this test needed at this time?

Public health officials have determined that Zika virus poses a potential public health emergency. Current information on Zika virus infection for healthcare providers, including case definitions and information about signs and symptoms, is available at http://www.cdc.gov/zika/hc-providers/index.html. All information and guidance, including those on Zika virus laboratory testing, may change as more data are gathered on this virus. Please check CDC's Zika virus website regularly for the most current information (http://www.cdc.gov/zika/index.html).

At this time, there are no FDA approved/cleared tests available that can detect Zika virus infection in clinical specimens in the U.S. Therefore, Siemens has developed the ADVIA Centaur Zika test to detect evidence of Zika virus infection.

The U.S. Secretary of Health and Human Services (HHS) has declared that circumstances exist to justify the emergency use of in vitro diagnostic tests for the detection of Zika virus and/or diagnosis of Zika virus infection. This EUA will terminate when the HHS Secretary's declaration terminates, unless FDA revokes it sooner.

## When should the ADVIA Centaur Zika test be performed?

Anti-Zika IgM is typically detectable starting soon after onset of symptoms and is reliably detectable for approximately 12 weeks following infection. If Zika virus infection is suspected based on CDC's published clinical and/or epidemiological criteria, the ADVIA Centaur Zika test may be ordered for patients whose blood specimen was collected after 8 days from likely risk of Zika virus exposure or post-onset of symptoms and should be performed according to the CDC-issued guidance (http://cdc.gov/zika/laboratories/lab-guidance.html). The algorithms included within the guidance illustrate the appropriate Zika testing approach based on the presence of signs and symptoms, pregnancy status, and the time between onset of symptoms or suspected

exposure and specimen collection.

As disease manifestations of dengue, other flavivirus, and chikungunya virus infections can resemble those of Zika virus infection, additional testing for these viruses should be considered in the context of the epidemiological setting to aid in differentiating dengue, other flavivirus, and chikungunya virus infections from Zika virus infections. Please contact your state or local health department to facilitate testing.

As of September 18, 2017, serum is the primary diagnostic specimen for Zika virus RNA and serologic testing, and should be the priority specimen for collection and testing with the ADVIA Centaur Zika test. The ADVIA Centaur Zika test has been authorized for use with human serum and plasma (EDTA or lithium heparin) specimen types. However, confirmatory testing requires the use of serum samples. Therefore, serum is the primary diagnostic specimen for Zika virus RNA and serologic testing, and should be the priority specimen for collection and testing with the ADVIA Centaur Zika test. If plasma specimens are used with the ADVIA Centaur Zika test, a patient-matched serum specimen should also be collected, or if this is not possible, an additional serum specimen should be collected soon after the original specimen.

Specimens tested with the ADVIA Centaur Zika test should be collected after 8 days post-onset of symptoms or likely risk of Zika virus exposure. If a specimen is collected prior to 8 days post-onset of symptoms or likely risk of Zika virus exposure the patient should be asked to return and provide a second blood specimen collected at least 7 days after the initial blood specimen was collected. Specimens should be collected with appropriate infection control precautions and according to the manufacturer's instructions for the specimen collection device, handling, and storage. Serum should be collected in serum separator tubes and centrifuged after collection to reduce the likelihood of hemolysis. Additional guidance for collection of body fluid specimens for Zika diagnostic testing may be found at: https://www.cdc.gov/zika/laboratories/test-specimens-bodyfluids.html.

**How should results from the ADVIA Centaur Zika test be interpreted?**

The ADVIA Centaur Zika test consists of the ADVIA Centaur Zika Ab and the ADVIA Centaur Zika IgM assays. Based on the results interpretation algorithm, the ADVIA Centaur Zika test may give one of three possible results: (1) Presumptive Zika Positive, (2) Negative for IgM antibodies to Zika virus, or (3) Negative for antibodies to Zika virus

- **Specimen tests Positive with the ADVIA Centaur Zika test (i.e., Presumptive Zika Positive)**

  A positive (i.e., Presumptive Zika Positive) result from the ADVIA Centaur Zika test indicates that anti-Zika IgM antibodies were detected in the patient's specimen. Confirmation of ADVIA Centaur Zika test positive results requires additional testing by CDC or by qualified laboratories designated by CDC and in consultation with CDC, using the CDC-issued algorithm published in the CDC laboratory guidance found at: http://cdc.gov/zika/laboratories/lab-guidance.html.

  Laboratory test results should always be considered in the context of clinical observations, epidemiological information, and travel history in making a final diagnosis and patient management decisions. For guidance on Zika virus, please refer to http://www.cdc.gov/zika/hc-providers/index.html.

  Presumptive Zika Positive ADVIA Centaur Zika test results are not definitive for diagnosis of Zika virus infection and must be confirmed with additional testing and/or consideration using the latest CDC testing algorithms for the diagnosis of Zika virus infection before making healthcare management or treatment decisions for the

patient. It is possible that the ADVIA Centaur Zika test may generate positive results in patients with a history of non-Zika flavivirus infections or in patients who have received yellow fever or Japanese encephalitis vaccination, which may make it difficult to identify which flavivirus is causing the patient's current illness. In the event of a false positive result, risks to patients could include any or all of the following: the impaired ability to detect and receive appropriate medical care for the true source of symptoms; in the case of pregnant women, an unnecessary increase in the monitoring of a woman's pregnancy; or other unintended adverse effects.

Due to cross-reactivity of anti-dengue IgM and IgG antibodies in tests to detect recent Zika virus infection, it may be difficult to determine the specific flavivirus causing the recent infection in patients with a history of flavivirus infection or in those who reside in areas where Zika and/or dengue virus have been known to circulate. Due to this limitation, the plaque reduction neutralization test (PRNT) is not currently routinely recommended for confirmation of ADVIA Centaur Zika test results in Puerto Rico. Please refer to CDC guidance, including the CDC laboratory guidance (http://www.cdc.gov/zika/laboratories/lab-guidance.html) for additional information about diagnostic testing recommendations in the U.S. and its territories.

In the U.S. and its territories, Zika virus infection and disease (non-congenital and congenital) are nationally notifiable conditions and should be reported to the local or state health department. For guidance on Zika virus, please refer to http://www.cdc.gov/zika/hc-providers/index.html.

While there is an established association between Zika virus infection during pregnancy and microcephaly, detection of anti-Zika IgM antibodies in specimens collected from a pregnant woman does not provide definitive information about the health of her fetus and does not indicate imminent harm to her fetus. If a pregnant woman is diagnosed with Zika virus infection based on detection of anti-Zika IgM antibodies, issues such as timing of infection during the course of pregnancy, presence of symptoms and other factors may help determine the risk to her fetus.

- **Specimen tests Negative with the ADVIA Centaur Zika test (i.e., Negative for IgM antibodies to Zika virus or Negative for antibodies to Zika virus)**

  A negative result by the ADVIA Centaur Zika test (i.e., Negative for IgM antibodies to Zika virus or Negative for antibodies to Zika virus) does not rule out Zika virus infection, particularly if testing is conducted prior to 8 days post-onset of symptoms (before anti-Zika antibody levels are expected to become detectable by the test) or more than 12 weeks after the infection is thought to have occurred (as anti-Zika IgM antibody levels are expected to drop). As with any test, providers must consider the patient's likelihood of exposure and the possibility of false laboratory results when making treatment or other patient management decisions.

  Absence of laboratory evidence of Zika virus infection cannot definitively rule out Zika virus infection in persons with epidemiological risk factors. All results should be considered in the context of clinical signs and symptoms, exposure risk and time since symptom onset, or in the absence of symptoms, time since exposure. Conversely, a result that is negative for IgM antibodies to Zika virus or negative to antibodies to Zika virus in an asymptomatic patient with a lower likelihood of exposure (e.g., a short term traveler to an affected area) may suggest the patient is not infected.

Guidance for healthcare providers, including those caring for pregnant women and women of reproductive age with possible Zika virus exposure is available on the CDC website: http://www.cdc.gov/zika/hc-providers/clinical-guidance.html.

## Reporting Adverse Events

You should report adverse events, including problems with test performance or results, to MedWatch at http://www.fda.gov/Safety/MedWatch/default.htm, by completing and submitting the online FDA Form 3500 for Health Professionals (available at https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home) or by calling 1-800-FDA-1088.

## All patients should receive the Fact Sheet for Patients: Understanding Results from the ADVIA Centaur® Zika Test

## Contact Information for the Manufacturer:

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Tarrytown, NY, USA, 10591
Phone: 877-229-3711

Any significant new findings that negatively impact the performance of the test and that are observed during the course of the emergency use of the ADVIA Centaur® Zika Test will be made available at https://my.healthcare.siemens.com/services.

## References

1) Rasmussen, S.A., Jamieson, D.J., Honein, M.A., Petersen, L.R. Zika Virus and Birth Defects – Reviewing the Evidence for Causality. New England Journal of Medicine, May 19, 2016; 374:1981-1987. DOI: 10.1056/NEJMsr1604338.
2) CDC Website - http://www.cdc.gov/zika/