

**Title: TIVICAY, TRIUMEQ, JULUCA and DOVATO (dolutegravir; abacavir, dolutegravir and lamivudine; dolutegravir and rilpivirine; dolutegravir and lamivudine): updated information on neural tube defects reported in Tsepamo Study, Botswana.**

Dear Healthcare Professional:

ViiV Healthcare would like to update you on new information regarding the potential safety issue related to neural tube defects (NTDs) in infants born to women with exposure to dolutegravir-containing regimens *at the time of conception* identified from the Tsepamo birth outcomes surveillance study in Botswana.

The preliminary unscheduled analysis in May 2018 reported 4 NTD cases out of 426 infants born to women with exposure to a dolutegravir-containing regimen at conception, representing a prevalence of 0.94% (95% CI 0.37%, 2.40%) compared to an expected background rate of approximately 0.1%.<sup>1</sup>

In the updated and prescheduled analysis reporting events from 15 August 2014 through 31 March 2019, a total of 5 NTD cases out of 1,683 deliveries to women taking dolutegravir at conception have been reported. This represents a prevalence of 0.30% (95% CI 0.13%, 0.69%) compared with 15 cases in 14,792 deliveries (0.10%, 95% CI 0.06%, 0.17%) in which the women had taken non-dolutegravir-containing antiretroviral regimens at conception, a difference of 0.20% (95% CI 0.01%, 0.59%).<sup>2</sup>

In the same study, one infant out of 3,840 (0.03%) deliveries to women who started dolutegravir-containing regimens during pregnancy had an NTD, compared with three infants out of 5,952 (0.05%) deliveries to women who started non-dolutegravir-containing regimens during pregnancy.

In view of the latest data from the Tsepamo study and all other available data, ViiV Healthcare has updated its recommendations for the use of dolutegravir-containing products as follows:

- Women of childbearing potential (WOCBP) should undergo pregnancy testing before initiation of dolutegravir
- WOCBP who are taking dolutegravir who are not planning pregnancy should be advised to use effective contraception throughout treatment
- In WOCBP who are actively seeking to become pregnant, or if pregnancy is confirmed within the first trimester while on dolutegravir, the risks and benefits of continuing dolutegravir versus switching to another antiretroviral regimen should be assessed and switching to an alternative regimen should be considered.

- Dolutegravir should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus

### **Supporting information**

- The Tsepamo study is an NIH/NICHHD-funded birth outcomes surveillance study conducted by the Botswana-Harvard AIDS Institute Partnership in Botswana. The two primary aims of the study are (1) to evaluate adverse birth outcomes by HIV-status and antiretroviral therapy regimen, and (2) to determine if there is an increased risk of NTDs among infants born to mothers exposed to efavirenz (EFV) from conception.
- Dolutegravir was tested in a complete package of reproductive toxicology studies conducted by ViiV Healthcare/GlaxoSmithKline, including embryofetal development studies, and no relevant findings were identified.
- Data analysed to date from other sources including the Antiretroviral Pregnancy Registry (APR), clinical trials, and postmarketing data are insufficient to address the risk of neural tube defects with dolutegravir.
- There is no evidence of increased risk of other adverse birth outcomes when dolutegravir is started after the first trimester of pregnancy.

### **Information on Neural Tube Defects**

- The neural tube is the foundation of the spinal cord, brain and the bone and tissues that surround it. Neural tube defects occur when the neural tube fails to completely form; this formation take place between 0 and 28 days after conception. Some of the known factors that increase the risk of neural tube defects include folate deficiency, certain medications, maternal obesity, diabetes or family history.

### **Action Being Taken by ViiV Healthcare**

- ViiV Healthcare will continue to evaluate the data for dolutegravir in pregnancy and explore further options for data generation.
- The product information for TIVICAY/TRIUMEQ/JULUCA/DOVATO has been updated accordingly and submitted, or is in the process of being submitted, to regulatory authorities for their review and approval.
- ViiV Healthcare is committed to communicate further data as it becomes available.

References:

1. Zash R, Makhema J, Shapiro R. Neural Tube Defects with Dolutegravir Treatment from the Time of Conception. *N Engl J Med.* 2018b; 379:979-981.
2. Zash R, Holmes L, Diseko M, Jacobsen D et al. Neural tube defects and antiretroviral treatment regimens in Botswana. *N Engl J Med.* 2019; DOI:10.1056/NEJMoa1905230