GlaxoSmithKline
Scientific Office
Saudi Arabia
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جلاكسوسميث كلاين
المكتب العلمي
المملكة العربية السعودية
س.ت. ١٠١٠٠٩٠٧٦١
ترخيص ٠٤-٠١-٠٠٤

Direct Healthcare Professional Communication

Date: 02 July 2018

Title: Tivicay® (Dolutegravir), Triumeq® (Dolutegravir /abacavir /Lamivudine): neural tube defects reported in infants born to women exposed to dolutegravir at the time of conception, in Tsepamo Study, Botswana.

Dear Healthcare Professional

ViiV Healthcare , in agreement with the Saudi Food and Drug Authority, would like to inform you of the following:

Key message:

A potential safety issue which has been brought to our attention by the Principal Investigator of the above study conducted in Botswana. The potential safety issue is related to Neural Tube Defect (NTD) cases in infants born to women with exposure to dolutegravir-containing regimens *at the time of conception* identified from a preliminary unscheduled analysis of the Tsepamo study (4 NTD cases out of 426 pregnancies on dolutegravir). This represents an incidence of about 0.9% with an expected background rate of about 0.1%.

In the same study, no infant born to a woman who started dolutegravir *during pregnancy* had a neural tube defect (N=0/2824).

While this safety signal is being evaluated, ViiV Healthcare recommends the following:

- In women of child bearing potential (WOCBP) pregnancy testing should be performed before initiation of treatment.
- WOCBP who are taking dolutegravir should avoid getting pregnant and should use effective contraception throughout treatment.
- In WOCBP who are actively seeking to become pregnant, it is recommended to avoid dolutegravir, unless a suitable alternative treatment option is not available.

Riyadh
P.O. Box 309
Riyadh 11411
T + 966 (12) 650 6771
F + 966 (12) 412 5066
www.gsk.com

- If a woman becomes pregnant while taking dolutegravir and the pregnancy is confirmed in the first trimester, it is recommended to switch to an alternative regimen unless there is not a suitable alternative treatment option available
- Dolutegravir should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

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Supporting information

- The Tespamo study is a birth outcomes surveillance study which is ongoing and further data will be captured during the ongoing surveillance. This information will help to further inform about the safety of dolutegravir during pregnancy. It is anticipated that birth outcomes from at least another 600 women who have already become pregnant and were on dolutegravir from prior to conception, will be captured in the ongoing surveillance over the next 9 months (May 2018 to February 2019).
- Dolutegravir was tested in a complete package of reproductive toxicology studies, including embryofetal development studies, and no relevant findings were identified.
- Although there is limited experience with the use of dolutegravir in pregnancy, the data analysed to date from all sources including Antiretroviral Pregnancy Registry (APR), clinical trials and post-marketing use has not indicated a similar potential safety issue. There is one additional case of NTD reported spontaneously from Namibia.
- There are no specific congenital abnormality signals (including NTD) from other sources when dolutegravir is started during 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 takes place between 0 and 28 days after conception. Neural tube defects may be related to factors such as folate deficiency, certain medications, maternal obesity, diabetes or family history.

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Action Being Taken by ViiV Healthcare

- ViiV Healthcare will continue evaluating the full body of data for dolutegravir in pregnancy, and explore further options for data generation. This includes evaluating several different databases to determine if other cases have been observed.
- ViiV Healthcare will also continue collaborating with the study investigators and key stakeholders including Regulatory Agencies
- The product information of TIVICAY/TRIUMEQ/JULUCA will be updated accordingly and further information will be communicated as appropriate.

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Current Label

The current labelling for dolutegravir containing products states:

> *There are no adequate and well-controlled studies of dolutegravir in pregnant women. The effect of dolutegravir on human pregnancy is unknown. In reproductive toxicity studies in animals, dolutegravir was shown to cross the placenta. Dolutegravir should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus.*

Call for Reporting:

NPC and GlaxoSmithKline Contact details for reporting adverse drug reactions as follows:

The National Pharmacovigilance and Drug Safety Centre (NPC):

Toll free number: 8002490000
Fax: +966 11 2057662
Email: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa/

GlaxoSmithKline safety:

Direct Tel: +966 12 653 6696
Mobile: +966 54 268 7301
email: gulf.safety@gsk.com
Local safety Responsible: doha.a.samargandi@gsk.com

Sincerely,

Ph. Doha Samargandi
Pharmacovigilance Specialist, QPPV KSA

GSK, Jeddah Head Office
Pharmacovigilance Qualified Person Responsible for Pharmacovigilance (QPPV)
Tel: +966126536666, E-mail: sa.aermi-saudi@gsk.com

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