Healthcare Professional Educational Guide for [Product Name] Use

1. Use of [Product Name] prescription:

[**PRODUCT NAME**] is the fixed dose combination of three antiretroviral drugs of dolutegravir 50mg, lamivudine 300mg and tenofovir disoproxil fumarate 300mg that is used for the treatment of HIV. A dolutegravir(DTG)-based HIV treatment was recommended by the World Health Organization as the preferred first-line regimen. This is due to clinical trials that have shown that DTG is more effective, better tolerated and more protective against treatment discontinuation from adverse drug reactions than efavirenz (EFV) at standard dose (600 mg/day). Further, DTG is associated with fewer drug interactions and has a higher genetic barrier to resistance to certain HIV strain mutations.

2. Information on congenital malformations / birth defects with the use of dolutegravir-based antiretroviral therapy

On May 18, 2018, the U.S. Food and Drug Administration and the World Health Organization announced that cases of neural tube defects have been reported in babies of women with HIV who were on treatment with dolutegravir (DTG) at the time of conception and during early pregnancy. The information comes from an observational study (the Tsepamo Study) of ART (DTG/TDF/FTC or efavirenz/TDF/FTC) in pregnant women in Botswana. [1] [2]

Initial data from this study, presented last year at IAS, reported that in women who started ART during pregnancy there were no congenital abnormalities seen in the 116 babies born to those who started dolutegravir/TDF/FTC during the first trimester and 1 birth defect among the babies of 396 women who started efavirenz/TDF/FTC in the first trimester. There were no differences in adverse birth defects in the larger numbers of women in the two groups who started ART The new data from the Tsepamo Study show that 0.9% of babies (4 of 426 babies) who were exposed to dolutegravir had neural tube defects compared with 0.1% of babies (14 of 11,173) who were exposed to other HIV medicines during pregnancy. The neural tube defects were reported only in babies of women who were taking dolutegravir at the time of conception--there were no reported neural tube defects among more than 2,500 babies born to women who began taking dolutegravir after conception.

3. Before initiating [Product Name] therapy, the following needs to be noted:

Healthcare Professional (HCP) experienced in the management of HIV:

- Discuss the risks involved in using [**Product Name**] with the patient (or parent/caregiver/responsible person).
- Exclude pregnancy in women of childbearing potential (by serum pregnancy test) before the first prescription is issued.
- Arrange for highly effective contraception for women of childbearing potential before the first prescription is issued.
- Complete the Annual Risk Acknowledgment Form with the patient (or parent/caregiver/ responsible person); give them a copy and send a copy to her GP, if different from the treating HCP.
- See the patient urgently (within days) in case of unplanned pregnancy or if she wants to plan a pregnancy.
- Ensure continuous use of highly effective contraception in all women of childbearing potential (consider the need for pregnancy testing if not a highly effective method).
- Check that all patients have an up to date, signed, Annual Acknowledgment of Risk Form each time a repeat prescription is issued.

4. Prescribing action for healthcare professionals in the treatment of adolescent girls and women of childbearing potential with [Product Name].

Existing female patients:

- Review women who may be of childbearing potential.
- Continue treatment with [**Product Name**] only if other treatments are ineffective or not tolerated and pregnancy is excluded by means of a negative pregnancy test.
- Discuss the need for her to be on an effective contraceptive method if she is to continue taking [**Product Name**]
- Ensure she understands the risks to the unborn child of using [**Product Name**] during pregnancy.
- Ensure she understands the need to comply with contraception throughout treatment and undergo pregnancy testing when required – e.g. if there is any reason to suggest lack of compliance or effectiveness of contraception.
- Complete and sign the Risk Acknowledgment Form (at initiation and every annual visit); give a copy to her.

New female patients:

- Start treatment with [**Product Name**] only if other treatments are ineffective or not tolerated and pregnancy is excluded by means of a negative pregnancy test.
- Assess potential for pregnancy.
- Ensure she understands the risks to the unborn child when using [**Product Name**] during pregnancy.
- Ensure she understands the need to comply with contraception throughout treatment and undergo pregnancy testing when required – e.g. if there is any reason to suggest lack of compliance or effectiveness of contraception.
- Complete and sign the Annual Risk Acknowledgment Form; give a copy to her.

Women of childbearing potential planning to become pregnant:

- Ensure she understands the risks of [**Product Name**] in pregnancy
- Switch [**Product Name**] to another alternative and effective antiretroviral option.
- Tell her not to stop contraception until the switch is achieved and she is no longer taking [**Product Name**]
- If switching is not possible refer for counselling about the risks.

Patients with an unplanned pregnancy:

- Women presenting with an unplanned pregnancy should have their treatment switched
- Women living with HIV who have to continue treatment in pregnancy (i.e. if switching to an alternative treatment is not possible) should be referred for appropriate monitoring.

5. Participating in the Antiretroviral Pregnancy Registry

The Antiretroviral Pregnancy Registry is intended to provide an early signal of any major teratogenic effect associated with a prenatal exposure to the products monitored through the Registry. The Registry is a voluntary prospective, exposure-registration, observational study designed to collect and evaluate data on the outcomes of pregnancy exposures to antiretroviral products. [3]

The Registry is a primary source for evaluating the use of antiretroviral products in pregnancy. Your contribution to this collaborative monitoring of exposures to antiretrovirals during pregnancy enables you to obtain information on available data in the Antiretroviral Pregnancy Registry Interim Report printed and distributed semi-annually.

Health care providers should report all exposures to ARV medications, including exposures for all women who were pregnant or conceived and used ARV medicines, to the Antiretroviral Pregnancy Registry via the following avenues:

Tel: +1 800 258 4263

Fax: +1 800 800 1052 / +44 1628 789 666

Email: SM_APR@INCResearch.com

Alternatively Healthcare professionals can contact Cipla for assistance in participating in the Antiretroviral Pregnancy Registry via the following avenues:

Tel: +27 21 943 4200

Email: drugsafetysa@cipla.com

Fax: +27 21 914 1587

References

1. U.S. Food & Drug Administration. FDA Drug Safety Communication: FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolutegravir (Juluca, Tivicay, Triumeq). 2018. Accessed: 10 August 2018. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm608112.htm
2. Zash R et al. 2018. Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study. Lancet Glob Health. Vol 6(7), pg804-e810.
3. The Antiretroviral Pregnancy Registry For Healthcare Providers. [Online]. Accessed 10 August 2018. Available at: http://www.apregistry.com/HCP.aspx