RWANDA FDA
Rwanda Food and Drugs Authority
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Kigali; 18/03/2022
Ref N°: DIS/1394/FDA/2022

MEDICINE SAFETY COMMUNICATION

Medicine: VALPROATE

RE: Warning on the potential risk of teratogenicity with Valproate

Reference is made to drug safety communication published by US FDA on children born to mothers who took Valproate products while pregnant risking to have impaired cognitive development.
Further reference is made to safety information published by Ghana FDA on restrictions to prevent the use of valproate medicines in women and girls of childbearing potential.

Valproate products are used to treat seizures, and manic or mixed episodes associated with bipolar disorder (manic-depressive disorder), and to prevent migraine headaches. They are also used on off-label (for unapproved uses) for other conditions, particularly for other psychiatric conditions. Babies exposed in utero to valproate are at high risk of serious developmental disorders (in up to 30-40% of cases) particularly neurodevelopment defects like spina bifida and/or congenital malformations (in approximately 10% of cases) like craniofacial defect including oral clefts, cardiovascular malformations, etc.

Children born to mothers who took valproate sodium or related products throughout their pregnancy tend to score lower on cognitive tests (IQ and other tests) than children born to mothers who took other anti-seizure medications during pregnancy. The risk of major development abnormalities is greatest during the first trimester, however it can occur with Valproate use throughout pregnancy. Currently, no established threshold dose below which no risk exists. Valproate products are assigned to Pregnancy Category D.

Valproate has the ability to cross the placenta from the apical (maternal interfacing) syncytiotrophoblast plasma membrane to the basal (fetal facing) circulation. In the majority of cases, Valproate accumulates in the circulation of the embryo, reaching a higher concentration than

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in the maternal blood; this may be responsible for causing toxicity and increased risk (approximately three-fold) of teratogenicity.

Rwanda FDA is warning health professionals, marketing authorization holders, and patients on the risk of teratogenicity and/or lower IQ in babies born to mothers who took valproate products including valproate sodium and related products, and valproic acid (brands) like (Depacon, Depakenine) when pregnant.

Information to Healthcare professionals

- Healthcare providers should weigh the benefits and risks of Valproate when prescribing this drug to women of childbearing age, particularly when treating a condition not usually associated with permanent injury or death. Alternative medications that have a lower risk of adverse birth outcomes should be considered.
- In pregnant women who have epilepsy valproate is contraindicated unless other treatments are ineffective or not tolerated.
- If the decision is made to prescribe valproate to women of childbearing age, healthcare professionals should recommend use of effective contraception for women who are not planning a pregnancy.
- Healthcare providers should inform women of childbearing age of the increased risk for adverse effects on cognitive development with prenatal valproate exposure.

Information to caregivers and patients

- Valproate should not be stopped without talking to a healthcare professional, even in pregnant women. Stopping valproate suddenly can cause serious health problems. Not treating epilepsy or bipolar disorder (manic-depressive disorder) during pregnancy can be harmful to women and their developing babies.
- Women of childbearing age who decide to take valproate should use effective birth control (contraception) while taking the drug. Women should talk to their healthcare professionals about the best kind of birth control to use while taking valproate.

Information to Marketing Authorization Holders

- Rwanda FDA requests Marketing Authorization Holders to add boxed information on the risk of teratogenicity and /or lower IQ in babies born to mothers who took Valproate products when pregnant.

Note: Patients and Healthcare Professionals are urged to report any suspected serious adverse drug reactions associated with Valproate products and other medicines to Rwanda FDA by completing ADR/AEFI reporting form accessible on the Rwanda FDA website via the link https://www.rwandafda.gov.rw/fileadmin/user_upload/RwandaFDA/Publications/Pharmacovigilance___Food_Safety_Monitoring/Forms/ADR_AEFI_Reporting_form.pdf and the filled form should be sent to the email: pv_sm@rwandafda.gov.rw

Sincerely,

18/3/20

Dr. Emile BIENVENU
Director General

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References

1. Ghana Food and Drugs Authority (2019) *Restrictions to prevent the use of valproate medicines in women and girls of childbearing potential.* Available at: http://www.fdaghana.gov.gh/img/reports/FDA%20DHCP%20Letter%20Valproate%20GS.pdf . (Accessed: 20 August 2021).

2. MEDSAFE-New Zealand Medicines and Medical Devices (2019) *Use of sodium valproate (Epilim) in girls and women – Change to indications and contraindications*. Available at: https://www.medsafe.govt.nz/safety/Alerts/Epilim.asp . (Accessed: 24 August 2021).

3. U.S. Food and Drug Administration (2018) *FDA Safety Drug Communication: Children born to mothers who took valproate products while pregnant may have impaired cognitive development*. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-children-born-mothers-who-took-valproate-products-while-pregnant-may#:~:text=FDA%20previously%20warned%20pregnant%20women,of%20an%20embryo%20or%20fetus. (Accessed: 26 August 2021).

4. World Health Organization (2018) *WHO Pharmaceutical Newsletter No. 5/2018*. Available at: https://apps.who.int/iris/bitstream/handle/10665/275697/WPN-2018-05-eng.pdf?sequence=1&isAllowed=y . (Accessed: 22 August 2021).

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