SAFETY ALERT

DRAP SAFTEY ALERT NO. 50

Safety Alert of risks associated with the use of Valproic Acid in Women and Girls of Childbearing potential and minor potential risk in male patients.

Date: 28th of April, 2024.

Target Audience.

- Manufacturers and importers of valproic acid;
- Healthcare Professionals; and
- Patients, Consumers or Caregivers.

Background.

The World Health Organization (WHO) in a safety statement dated 2nd of May 2023 alerted stakeholders to the revised guidance on the use of valproic acid (sodium valproate) for the treatment of epilepsy and bipolar disorder in women and girls of childbearing potential. It was informed that valproic acid (sodium valproate) should not be prescribed to women and girls of childbearing potential because of the high risk of birth defects and developmental disorders in children exposed to valproic acid (sodium valproate) in the womb. In women and girls of childbearing potential, lamotrigine or levetiracetam should be offered as first-line monotherapy for both generalized onset seizures and focal onset seizures.

For women and girls of childbearing potential who are currently prescribed valproic acid (sodium valproate), the WHO also stated that advice should be provided on the use of effective contraception, without interruption, during the entire duration of treatment. Information must be provided on risks associated with valproic acid (sodium valproate) use during pregnancy, pregnancy prevention and referral for contraceptive advice if they are not using effective contraception. Individual circumstances should be evaluated in each case when choosing the contraception method and involving the woman in shared decision-making. If a woman is planning to become pregnant, a person trained in the management of epilepsy/bipolar disorder in pregnant women should consider alternative treatment options. Women should be informed to consult their physician as soon as they are planning pregnancy and the need to urgently consult their physician in case of pregnancy. Every effort should be made to switch to appropriate alternative treatment before conception. If switching is not possible, the woman should receive further counselling regarding the risks of valproic acid (sodium valproate) for the unborn child to support her informed decision-making. A specialist should periodically review whether valproic acid (sodium valproate) is the most suitable treatment for the person.

NPC, DRAP, PM Health Complex, Chak Shahzad Islamabad +92 51 9255981 npc@dra.gov.pk

The EMA's safety committee (PRAC) in its meeting held on 8-11 January, 2023 recommended precautionary measures for the treatment of male patients with valproate medicines. These measures are to address a potential increased risk of neurodevelopmental disorders in children born to men treated with valproate during the three months before conception. In reaching its conclusion, the PRAC reviewed data from a retrospective observational study carried out by companies that market valproate as an obligation following a previous review of valproate use during pregnancy. The committee also considered data from other sources, including non-clinical (laboratory) studies and scientific literature, and consulted patients and clinical experts. The PRAC's latest recommendations come in addition to restrictions and other measures that are already in place to avoid valproate exposure in pregnancy because exposed babies are at high risk of malformations and developmental problems. These measures were endorsed following a referral of valproate and related substances in 2018. The measures at that time included a ban on the use of such medicines for migraine or bipolar disorder during pregnancy, and a ban on treating epilepsy during pregnancy unless there is no other effective treatment available.

PRAC also discussed a direct healthcare professional communication (DHPC) for valproate medicines which will be forwarded to the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). When adopted, the DHPC will be disseminated to healthcare professionals by the marketing authorization holders. The DHPC will inform healthcare professionals about the potential risk of neurodevelopmental disorders in children of fathers treated with valproate in the three months prior to conception. It is recommended that valproate treatment in male patients is started and supervised by a specialist in the management of epilepsy, bipolar disorder or migraine. Valproate treatment of male patients should be reviewed regularly to consider whether it remains the most suitable treatment, particularly when the patient is planning to conceive a child.

On 22nd January, 2024, the United Kingdom, medicine and Health Product Regulatory Agency (MHRA) through a drug safety update informed that new safety and educational materials had been introduced for men, women and healthcare professionals to reduce the harm from valproate, including the significant risk of serious harm to the baby if taken during pregnancy and the risk of impaired fertility in males. Healthcare professionals were advised to review the new measures and materials and integrate them into their clinical practice when referring patients and when prescribing or dispensing valproate. Healthcare professionals were advised that valproate must not be started in new patients (male or female) younger than 55 years unless two specialists independently consider and document that there is no other effective or tolerated treatment, or

there are compelling reasons that the reproductive risks do not apply. For the majority of patients, other effective treatment options are available. At their next annual specialist review, women of childbearing potential and girls receiving valproate should be reviewed using the revised valproate Annual Risk Acknowledgement Form. A second specialist signature will be needed if the patient is to continue on valproate, however subsequent annual reviews will only require one specialist general practice and pharmacy teams should continue to prescribe and dispense valproate and if required offer patients a referral to a specialist to discuss their treatment options.

Valproate has a high teratogenic potential. Exposure to valproate in pregnancy is associated with physical birth defects in 11% of babies and neurodevelopmental disorders in up to 30-40% of children, which may lead to permanent disability. Since 2018, valproate has been contraindicated in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme (PPP) are followed. The purpose of PPP was to ensure all women and girls are fully informed of the risks and the need to avoid exposure to valproate medicines in pregnancy through an annual review and signing a risk acknowledgement form.

In 2022, the Commission on Human Medicines (CHM) reviewed the latest data on the safety of valproate. The CHM heard from patients and other representatives about how valproate was being used and how the risks were currently managed. The CHM noted that data from the Medicine and Pregnancy Registry showed that pregnancies in England continue to be exposed to valproate. The CHM also considered other known risks of valproate, including the risk of impaired male fertility. The CHM considered pre-clinical data on possible transgenerational risks with prenatal exposure, as well as data from studies in juvenile and adult animals suggesting adverse effects on the testes. There are currently limited data available on many of these risks in humans and further studies are planned. However, the CHM noted many patients receiving valproate have other therapeutic options with fewer potential reproductive harms.

On 28th November 2023, MHRA issued a National Patient Safety Alert to instruct Integrated Care Boards (in England), Health Boards (in Scotland), Health Boards (in Wales), and Health and Social Care Trusts (in Northern Ireland) to prepare for the new risk minimisation measures by 31 January 2024. The new safety and educational materials support these measures. Due to the known significant risk of serious harm to a baby after exposure to valproate in pregnancy, these measures aim to ensure valproate is only used if other treatments are ineffective or not tolerated, and that any use of valproate in women of childbearing potential who cannot be treated with other medicines is in accordance with the Pregnancy Prevention Programme (PPP).

The CHM will consider further recent registry data which may suggest an increased risk of neurodevelopmental disorders in children whose fathers took valproate in the 3 months before conception. In the study, around 5 children in 100 born to fathers treated with valproate around conception were diagnosed with a neurodevelopmental disorder. This is compared to 3 in 100 children whose fathers were taking lamotrigine or levetiracetam around conception (two other anti-seizure medicines). As a precaution, male patients on valproate who are planning a family within the next year should speak to a healthcare professional about their treatment options. Moreover, MedSafe, Newzealand on 7th December 2023 informed that the data sheet and the consumer medicines information leaflet of sodium valproate (Epilim) have been recently updated with additional information use in people who can father children.

Action in Pakistan.

The case was discussed in the 4th meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) of the DRAP held on 26th of February, 2024 which decided the case as per Rule 10 (1) (h) (ii) of the Pharmacovigilance Rules, 2022 that registration holders of sodium valproate should update the contraindication not to prescribe sodium valproate-containing medicines in following situations: in pregnancy if there is no other effective or tolerated treatment available and individual benefit-risk assessment is performed and documented for each patient; and in women of childbearing potential aged under 55 years, unless there is no other effective or tolerated treatment available, followed by individual benefit-risk assessment and the patients are made aware of pregnancy prevention programme. Furthermore, also decided as per Rule 10 (1) (h) (vi) of the Pharmacovigilance Rules, 2022 registration holders should initiate an awareness Programme for Pregnancy Prevention (PPP) for sodium valproate-containing medicines. Similarly, as per Rule 10 (1) (h) (iv) of the Pharmacovigilance Rules, 2022, the PRAEC decided that registration holders should also update the warning and precaution section of the prescribing information/ label of sodium valproate-containing medicines by including information about high-risk of birth defects and neuro-developmental disorders in children exposed to valproic acid (sodium valproate) in the womb and about the minor potential risk of neurodevelopmental disorders in children of fathers treated with valproate in the three months before conception and as a precaution advise male patients on valproate who are planning a family within the next year should speak to a healthcare professional about their treatment options.

Therapeutic Goods.

Name: Valproate (sodium valproate/valproic acid) is authorised for use in epilepsy and bipolar disorder.

Advice for Healthcare Professionals.

Healthcare professionals are informed about the high risk of birth defects and neuro-developmental disorders in children exposed to valproic acid (sodium valproate) in the womb and about the minor potential risk of neurodevelopmental disorders in children of fathers treated with valproate in the three months before conception. Therefore, healthcare professionals are advised not to prescribe valproate-containing medicines in pregnant females if there is no other effective or tolerated treatment available and individual benefit-risk assessment is performed and documented for each patient. Likewise, it should also not be prescribed in women of childbearing potential aged under 55 years, unless there is no other effective or tolerated treatment available, followed by individual benefit-risk assessment and the patients are made aware of the pregnancy prevention programme. As a precautionary measure, healthcare professionals should speak to male patients on valproate-containing medicines who are planning a family within the next year about their treatment options.

Advice for Patients.

Patients are advised to not stop taking valproate or alter their dose without checking with their specialist first; if they stop taking valproate without their specialist's advice their condition may get worse. Further, it is also informed that valproate is associated with a significant risk of birth defects and neurodevelopmental disorders in children born to women who take valproate during pregnancy and the findings of a new study have suggested that there may be a minor increased risk of neurodevelopmental disorders in children of men who took valproate in the 3 months before conception. Therefore, women and girls of childbearing potential are advised to talk with their doctors if they are planning for pregnancy and otherwise as well. Likewise, healthcare professionals male patients on valproate-containing medicines who are planning a family within the next year may also talk with their doctors about their treatment options.

Guidelines for reporting Adverse Drug Reactions (ADRs).

Both healthcare professionals and patients are requested to report any suspected adverse drug reaction (ADRs) with valproic acid to the National Pharmacovigilance Centre (NPC), Drug Regulatory Authority of Pakistan (DRAP) through the Med Vigilance E-Reporting System available on the DRAP website. Similarly, ADRs can also be reported through Med Safety App which is available through the App Store (for iOS devices) and Google Play (for Android devices).

References.

- Minutes of the 4th meeting of the Pharmacovigilance Risk Assessment Expert Committee.
- WHO-Statement on the risks associated with the use of valproic acid (sodium valproate) in women and girls of childbearing potential.

NPC, DRAP, PM Health Complex, Chak Shahzad Islamabad | +92 51 9255981 | npc@dra.gov.pk

- MHRA-UK-Valproate: reminder of current Pregnancy Prevention Programme requirements; information on new safety measures to be introduced in the coming months.
- Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 8-11 January 2024 of EMA.

NPC, DRAP, PM Health Complex, Chak Shahzad Islamabad

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