Patient Safety and Quality Improvement Service

PATIENT SAFETY NOTICE

A Patient Safety Notice identifies potential patient safety issues requiring risk assessment at the local level to determine appropriate actions

Distributed to:

- **Hospital and Health Service Boards**
- **Hospital and Health Service Chief Executives**

We recommend you also inform:

- Patient Safety Officers
- Executive Directors of Medical Services
- Hospital and Health Services Safety and Quality Staff
- Directors of Mental Health
- Directors of Neurology
- Directors of General Medicine
- Directors of Emergency Departments
- Directors of Obstetrics & Gynaecology
- Directors of Pharmacy

Action required by:

- Hospital and Health Service Boards
- Hospital and Health Service Chief Executives

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For Internal Use Only

Persons receiving this Patient Safety Notice should **NOT** take any further action unless the affected goods are/were supplied to or are/were in use in the Hospital and Health Service in which they work.

Subject:	Valproate – strengthened recommendations to avoid teratogenic effects and neurodevelopmental disorders
Issued by:	Medication Services Queensland
Issue Date:	15 April 2019
Approved by:	Chief Health Officer and Deputy Director-General, Prevention Division Signature: **SIGNED**

Purpose

The purpose of this Patient Safety Notice is to:

- remind clinicians that valproate (sodium valproate, valproic acid) has established teratogenic and developmental risks to babies, in up to 40% of exposed pregnancies.
- Alert clinicians to recommendations to prevent valproate exposure in pregnancy including the increased need to discuss and document contraception and pregnancy plans (**see recommendations below**).

Recommendations

Avoid valproate whenever possible in female adolescents and women of childbearing potential, unless alternative treatments are proven ineffective or not tolerated, OR there is no suitable alternative (risk-benefit analysis); AND effective contraception** is in place.

When valproate treatment is deemed essential or unavoidable by a consultant specialist:

1. Ensure management of therapy is under a specialist prescriber—consultant psychiatrist or a consultant neurologist—where the benefit and risk can be reconsidered at regular treatment reviews (minimum annually).

2. Exclude pregnancy via serum pregnancy test before commencing therapy. Assess and document the potential of becoming pregnant. It is safest to assume pregnancy potential including in women who are not currently sexually active.

3. Ensure treatment with valproate is a shared decision with the patient, weighing risks and benefits for a particular disorder. Ensure the patient understands fully the serious risks in pregnancy.

4. Use the lowest effective dose of valproate.

5. Explain and document the need for effective contraception**. Provide and counsel on OR refer the patient for an appropriate and effective contraception method ensuring appropriate evaluation of individual circumstances in each case.
6. Counsel the patient about the known risks of valproate therapy and their responsibilities to ensure avoidance of pregnancy via effective contraception**, and the need for urgent medical advice if there is a suspected problem with contraception or any suspicion of pregnancy. The patient also needs to understand the importance of working with their specialist if pregnancy is being considered and the risks to the patient if self-discontinuation occurs.
7. Document the outcomes of any discussions and decisions including: need for valproate treatment, and contraception plans. Consider a formal risk acknowledgment process, as an example see the risk acknowledgment form available at https://www.gov.uk/guidance/valproate-use-by-women-and-girls (NB. this document is from the UK).
8. Encourage patients to have a consistent general practitioner / primary care provider to ensure appropriate monitoring, facilitation of continuity of contraception, and if recommended pregnancy testing at regular (monthly) intervals during treatment with valproate.
9. In the case of an unplanned pregnancy in a patient on valproate therapy, the clinician should contact the patient's usual neurologist / psychiatrist urgently to discuss the management plan, including the potential for the safe reduction of dose. Urgent referral for specialist review (within a couple of days) should also be made.

[Adapted, following local consultation, from UK MHRA Guidance: Valproate use by women and girls, resources including: 'Guide for Healthcare Professionals'(1), 'Valproate annual risk acknowledgement form'(2), 'Drug Safety Update'(3) available via the following link https://www.gov.uk/guidance/valproate-use-by-women-and-girls]

Issue/Hazard

Although valproate has been available in Australia since the 1960s(4), the risks to unborn children of *in utero* valproate exposure is increasingly understood, and warnings to avoid use during pregnancy are being strengthened.(5) The risk includes congenital malformations and developmental disorders, available data show that the risk is dose dependent(6-10); in general with greater risks at doses above 600mg/day.(7, 8) A threshold dose below which no risk exists cannot be established based on available data(1), these risks increase dramatically as the dose escalates.(6-9) [Refer to references for further information]

1. Congenital malformations

   Use of valproate in pregnancy leads to congenital malformations in around 10 in every 100 babies (compared with the general population risk of about 2-3%).(1, 3, 5) Risk of malformations includes the following: neural tube defects, facial dysmorphism, cleft lip and palate, cardiac, renal and urogenital defects, limb defects, craniostenosis and multiple anomalies involving various body systems.(1)

2. Developmental disorders

   Neurodevelopmental disorders occur in approximately 30 to 40 in every 100 children following exposure to valproate *in utero.*(3) The effects can include delays in the child's early development such as talking and walking, as well as lower intellectual ability, poor language skills and memory problems.(1) There is limited data on the long term outcomes(1), however, a study assessing cognitive outcomes of fetal exposure to antiepileptics showed cognitive deficits in children with fetal exposure to valproate at 6 years of age.(11)

   In utero valproate exposure is associated with an increased risk of autism spectrum disorder and autistic disorder (childhood autism).(12) Additionally, limited data suggest an increased risk of developing symptoms of attention deficit/hyperactivity disorder in children exposed to valproate *in utero*.(13)

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Background

Valproate is currently marketed in Australia under several brand names including Epilim®, Valpro®, Valprease® (other generic brands are also available).[14] It is Category D according to the Australian categorisation system for prescribing medicines in pregnancy, which is defined as "*Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects*".[15] Therefore, the manufacturer's product information includes pregnancy as a contraindication.[15, 16]

In 2018, the UK introduced strengthened regulatory measures – the 'valproate pregnancy prevention' programme – this followed a 2017 European Union (EU) scientific review on the topic which recommended new measures to avoid valproate exposure in pregnancy.[3]

Recent Queensland hospital's retrospective audits of contraceptive use by women of child-bearing potential taking valproate in the mental health setting identified that of the patients audited, fewer than 20% had documentation relating to discussion and/or prescription of contraception.

****Notes on contraception for this patient population**

- Highly effective contraception is considered (by UK guidance) to be a user independent method such as the long acting reversible contraceptives (LARC).[1, 3, 17]
    - LARC are the most effective reversible methods of contraception available.[18]
    - LARC currently available in Australia[18]
        - Mirena® (levonorgestrel)—intrauterine system
        - Implanon® NXT (etonogestrel)—progestogen-only subdermal implant [consider potential drug interactions, efficacy reduced by some drugs; e.g. enzyme inducing drugs may decrease contraceptive efficacy[19, 20]]
        - Copper intrauterine devices
    - Injectable contraception [depot medroxyprogesterone acetate (DMPA)] is considered by Australian guidance to be user-dependent (requires the user to return every 12 weeks for a repeat dose) and is no longer considered a LARC method because it is less effective than intrauterine contraception and the subdermal implant.[18]
- UK guidance advises if a user independent form is not used, two complementary forms of contraception including a barrier method should be used and regular pregnancy testing considered.[1, 3, 17]
- Contraception should continue uninterrupted during the entire duration of treatment with valproate.[1]

Action required by Hospital and Health Services:

1. Undertake a risk assessment to determine if the issues outlined in the Patient Safety Notice exist in your facility.
2. Disseminate this Patient Safety Notice to all relevant staff including at access points where patients prescribed valproate access the facility.
3. Consider how safety measures to reduce inappropriate prescribing of valproate in female patients of childbearing potential and use for non-seizure related indications may be implemented.[4]
4. Consider how the facility can document the decision process, risks and responsibilities of continuing valproate in female patients of childbearing potential.
5. Consider if there are local barriers to accessing LARC contraception (e.g. availability of services with clinicians with the specific skills, training and ongoing practice in insertion of these devices) and how these may be overcome.

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Management Review: For local risk management.

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