Tablet Press Extra
The prescribing newsletter for GPs, nurses and pharmacists
NHS Northamptonshire ICB
September 2024

Prescribing of Valproate Containing Medicines

Background

- In January 2024 a change to the regulations governing prescribing of valproate containing medicines stated that they should not be started in new patients (male or female) younger than 55 years unless two specialists independently agree and document that there is no other effective or tolerated treatment or there are compelling reasons that the reproductive risks do not apply.
- Valproate should not be used in female patients of childbearing potential unless there is a pregnancy prevention programme in place (PPP) https://www.gov.uk/guidance/valproate-use-by-women-and-girls . This is designed to make sure that patients are fully aware of the risks and the need to avoid becoming pregnant.
- The reason for this is that studies have found if valproate is taken during pregnancy, up to 4 in 10 babies are at risk of developmental disorders and approximately 1 in 10 are at risk of birth defects. Male patients on valproate are at risk of fertility problems and their children have an increased risk of developmental disorders.

Secondary care responsibilities for patients being prescribed valproate containing medicines (sodium valproate, valproate semi-sodium or valproic acid)

- **New female patients of childbearing potential.** Two specialists must independently agree and document on the Annual Risk Acknowledgement Form (ARAF) that there are no other effective or tolerated treatments **or** there are compelling reasons that the reproductive risks do not apply.
- **Existing female patients of childbearing potential**. At the next annual specialist review, review and complete the revised valproate ARAF. Two specialists must independently agree and document that there is no other effective or tolerated treatments **or** there are compelling reasons that the reproductive risks do not apply, if the patient is to continue with valproate.
- Subsequent annual reviews require only one specialist signature unless the patient's situation changes.
- An ARAF should be completed unless there are compelling or permanent reasons why the patient is not at risk of pregnancy in which case Step 1 of the ARAF must be completed and the reasons documented. Further annual ARAFs are not required unless the patient's situation changes.
- Use of valproate for migraine or bipolar disorder is contraindicated in pregnancy and it should only be used for epilepsy in pregnancy if there is no other effective treatment available.
- All patients considered to be of childbearing potential should be on the PREVENT pregnancy prevention programme.
- The Royal Colleges have jointly produced a helpful Guidance Document on Valproate Use in Women and Girls of Childbearing Years https://www.rcpch.ac.uk/sites/default/files/2021-01/Pan_College_Guidance_Document_on_Valproate_Use%20V2.1.pdf
- **New Male Patients under 55 years.** Two specialists must independently agree and document that there are no other effective or tolerated treatments **or** there are compelling reasons that the reproductive risks do not apply if the patient is to be started on valproate.

☎ 01604 651359

Primary Care responsibilities

- Primary care clinicians are responsible for the safe prescribing of valproate, checking that the appropriate reviews have been carried out by the secondary care team responsible for the initial prescribing of the Valproate medication and referring the patient to secondary care if an ARAF is not available
- Any patient who does not have a current ARAF in place can be referred to:
  Neurology NGH: ngh-tr.epilepsysodiumvalproate@nhs.net
  Neurology KGH: mark.jeffries2@nhs.net
  Paediatrics NGH: rebecca.currington1@nhs.net
  Paediatrics KGH: keshav.kallambella@nhs.net
  NHfT: James.Tanner@nhft.nhs.uk
- Patients not currently under the care of a specialist team should be referred via existing electronic referral routes.
- If discharged from specialist follow-up, an attempt should be made to re-engage with the service that originally started valproate.
- If patients are under specialist teams outside Northamptonshire, notify teams directly.
- If valproate has been initiated by a GP, treatment should be reviewed. If it is to be continued, the GP should complete the ARAF and advise the patient regarding contraception. **Note that GP completion of the ARAF is not in compliance with the MHRA alert.**
- Regardless of the presence of an ARAF, GPs are responsible for their own prescribing and for advising patients of the risks of a valproate affected pregnancy.
- GPs are responsible for ensuring the patient has access to **highly effective** contraception. See Appendix 1 for information on **highly effective** contraception
- If GPs are unable to provide suitable **highly effective** contraception, the Northamptonshire Integrated Sexual Health Services (NISHH) provide specialist care for basic contraception (under 19s only) and complex contraception (all ages). The service should be contacted directly. Phone no 01604 609766. They accept self-referral to the sexual health service but if any woman needs fast-tracking for provision of implants or coils send a provider referral to either:
  - NGH hub: nish.ngh@nhs.net Phone 030000 274100
  - Ashwood Centre, St Mary's Hospital hub: Ashwood.centre@nhs.net Phone 03000 270110

  They will then contact the individual to book an appointment.

- **If the patient is not considered to be at risk of pregnancy, (for example if they receive 24 hour care in a safe environment), Step 1 of the ARAF should still be completed and a copy filed in the GP record. This does not need to be repeated unless the patient's circumstances change.**

Additional Information

- Patients on valproate who are considering a planned pregnancy should be referred to their specialist. Pre-conception counselling is also available from the NHFT peri-natal team
- The GMC, GPHC and NMC have jointly developed a case study on treating women that take valproate https://www.gmc-uk.org/ethical-guidance/learning-materials/risks-of-sodium-valproate
- The PAN-college guidance document https://www.rcpch.ac.uk/sites/default/files/2021-01/Pan_College_Guidance_Document_on_Valproate_Use%20V2.1.pdf contains helpful advice on women who do not engage with services or who do not wish to use highly effective contraception.
- Advice on pregnancy testing and contraception for pregnancy prevention during treatment with medicines of teratogenic potential is available from https://assets.publishing.service.gov.uk/media/5c936a4840f0b633f5bfd895/pregnancy_testing_and_contraception_table_for_medicines_with_teratogenic_potential_final.pdf
- When a copy of an ARAF is received in a GP practice it is helpful to add a "pharmacy text note" to the drug record in Systm1 or EmisWeb including the expiry date of the ARAF. This will also ensure visibility on the Summary Care Record.
- The presence of an ARAF should be READ or SNOMED coded

  READ codes

  Y2f16 Pregnancy prevention programme started (use when ARAF is received from secondary care and ongoing annual reviews are required)
  Y362e ARAF completed
  Y38a6 referral to secondary care for completion of Valproate ARAF
  Y2f18 Pregnancy prevention programme not needed (use when ARAF is received from secondar care and ongoing reviews are not needed eg patient is of childbearing age but has had a hysterectomy).

  SNOMED codes

  1129771000000103 Pregnancy prevention programme started (use when ARAF is received from secondary care and ongoing annual reviews are required)
  1366401000000107 ARAF completed
  1366381000000107 referral to secondary care for completion of Valproate ARAF
  1112979100000104 Pregnancy prevention programme not needed (use when ARAF is received from secondary care and ongoing reviews are not needed eg patient is of childbearing age but has had a hysterectomy).

- ARDENs templates are available which will automatically add codes to the GP record
- ARDENs also supports a CQC report on teratogenic drugs "*On teratogenic drugs in childbearing age – review as prescribed Valproate / Carbimazole / Modafinil / Topiramate / Pregabalin"* which may help practices to identify relevant patients.
- In Eclipse a report is available in the QIC section CQC Live

Appendix 1: Contraceptive advice for women and girls on valproate

- 'Highly effective' contraceptives in this context include the long-acting reversible contraceptives (LARC): copper intrauterine device (Cu-IUD), levonorgestrel intrauterine system (LNG-IUS) and progestogen-only implant (IMP) and male and female sterilisation, all of which have a failure rate of less than 1% with typical use. Depot medroxyprogesterone acetate (DMPA - Depo-Provera and Sayana Press) is not regarded as highly effective due to the potential for pregnancy if the injection is delayed. The Faculty of Sexual and Reproductive Healthcare (FSRH) has advice about contraceptive options for patients on known teratogenic agents link as does the MHRA link with a useful aide memoire table link
- Patients should be advised that no method of contraception has 100% efficacy.
- The typical use failure rate of combined hormonal contraception (CHC) and the progestogen-only pill (POP) is 9%; for progestogen-only injectable DMPA it is 6%. Given the importance of avoiding pregnancy during use of known teratogenic drugs or drugs with potential teratogenic effects, the CEU recommends that in this situation women using CHC, POP or DMPA should be advised to use additional barrier methods (e.g. condoms). (Note that women using CHC or POP must not take any interacting drugs that could reduce contraceptive effectiveness. Many anti-epileptic medications will reduce contraceptive effectiveness). Use of barrier methods, withdrawal and fertility awareness methods alone is not recommended.

- The FSRH has a helpful table of failure rates of contraceptive methods with typical and perfect use. Highly effective methods highlighted in yellow.

Percentage of women experiencing an unintended pregnancy within the first year of use with typical use and perfect use (modified from Trussell et al.)

Method	Typical use (%)	Perfect use (%)
No method	85	85
Fertility awareness-based methods	24	0.4–5
Female diaphragm	12	6
Male condom	18	2
Combined hormonal contraception (CHC) including combined contraceptive pill, transdermal patch and vaginal ring	9	0.3
Progestogen-only pill (POP)	9	0.3
Progestogen-only injectable depot medroxyprogesterone acetate (DMPA)	6	0.2
Copper intra-uterine device (Cu-IUD)	**0.8**	**0.6**
Levonorgestrel 13.5mg/19.5mg/52mg intrauterine system (LNG- IUS)	**0.2**	**0.2**
Progestogen-only implant (IMP)	**0.05**	**0.05**
Female sterilisation	0.5	0.5
Vasectomy	0.15	0.1

- The Royal College of Obstetrics and Gynaecology (RCOG) guidelines state that contraception should be continued until menopause, **defined as two years after the last natural menstrual period in women aged under 50 and one year after the last natural menstrual period in women aged over 50. If menopause cannot be confirmed, contraception should be continued until 55.**