

## Medicines Guideline: On Valproate prescribing for bipolar disorder including use in women of child-bearing potential (MG08)

Document author	Assured by	Review cycle
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This guidance should be read in conjunction with the following Trust documents:

- Medicines Policy [P060](#)
- Procedure for Prescribing Medicines Med02

## Contents

1. Background .....	2
2. Dose equivalence .....	2
3. Use in women of child bearing potential .....	2
3.1 Risks .....	3
3.2 Advice to patients .....	3
4. Prescriber's responsibilities .....	3
5. General prescribing advice.....	4
6. Pharmacy responsibilities .....	4
7. References and further reading .....	4

## 1. Background

Valproate is a salt – sodium or semi sodium of valproic acid. It is used in the management of epilepsy (sometimes for seizure prophylaxis in patients maintained on high clozapine plasma levels) as well as mania. In 2009, the European Medicines Agency conducted a [review](#) of the safety of valproate in the treatment of manic episodes in bipolar disorder. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of valproate in bipolar disorder outweigh their risks, and that all marketing authorisations for medicines containing valproate throughout Europe should be amended to include the treatment of manic episodes in bipolar disorders when lithium is contraindicated or not tolerated. Despite this recommendation, only Depakote<sup>®</sup> (semi-sodium valproate) and Episenta<sup>®</sup> (sodium valproate m/r) lists this as a licensed indication. In practice however, sodium valproate is commonly used to treat bipolar disorder.

This guideline aims to highlight areas that need to be given careful consideration when prescribing valproate, especially in women of child bearing potential and also when switching between preparations.

## 2. Dose equivalence

Valproic acid is the active moiety that is released from both semi-sodium and sodium valproate. Semi-sodium valproate (Depakote) releases marginally more valproic acid per gram than sodium valproate. E.g. 500mg of Depakote releases 500mg of valproic acid while 500mg of sodium valproate gives 433mg valproic acid. It is sometimes necessary to switch between the different preparations to either aid compliance (e.g. use of liquid) or to allow a tailored dose titration.

The conversion rate is as follows:

**1000mg of semi-sodium valproate (Depakote) = 1160mg Sodium valproate (e.g. Epilim)**

Due to the strengths of the preparations available, you may need to round up or down depending on the chosen valproate preparation. Depakote comes in two strengths – 250mg and 500mg while sodium valproate comes in various strengths (see below) as well as liquid.

### Sodium valproate

Crushable tablets: 100mg

Gastro resistant (e/c) tablets: 200mg, 500mg

Modified release (m/r) tablets: 200mg, 300mg, 500mg

Modified release capsules: 150mg, 300mg

Modified release granules: 50mg, 100mg, 250mg, 500mg, 750mg, 1000mg

Liquid: 200mg/5ml

It is essential that when prescribed, the salt of valproate is clearly stated as well as the form e.g. m/r for modified release preparations.

## 3. Use in women of child bearing potential

Valproate is a known teratogen in humans. It is therefore *not recommended* for use in women of child bearing potential either for an acute episode or for the long term management of mania [NICE [CG185](#)]. It should only be used when the assessed benefits are considered to outweigh the risks.

Women who have mania are likely to be sexually disinhibited and thereby have a higher than average risk of pregnancy (unplanned pregnancy risk in the general population is 50%). Where valproate is considered the most appropriate treatment choice, it should be ensured that the patient has adequate contraception in place.

Sodium valproate impairs the production of the active metabolite of folate. It is therefore currently recommended that women who take valproate also take high dose folic acid (5mg daily) prior to conception and throughout the first trimester. Patients should, however, be counselled that while folic acid helps to prevent neural tube defects that may affect any pregnancy, there is currently no strong scientific evidence that folate supplementation protects against neural tube defects and other congenital malformations or neurodevelopmental problems caused by valproate [[UKTIS – valproate](#)].

The risks of using valproate must be explained to all women of child-bearing potential and consent given/ documented before it is initiated.

### 3.1 Risks

The risks can be dose related therefore the minimum effective dose must be used at all times. About 10% of pregnant women taking valproate will have a baby with a birth defect compared to a 2-3% risk in the general population. The risks include:

- Congenital malformations e.g. neural tube defects, particularly spina bifida, cardiac defects, orofacial clefts, and hypospadias. Malformations of the skull, limb and digits have also been documented
- Serious developmental disorders e.g. difficulty with language, memory, slow to walk/talk (up to 30-40% of cases)
- Neurodevelopmental disorders including autism spectrum disorders, cognitive impairment (such as lower IQ), motor delay, and behavioural problems have also been reported.

### 3.2 Advice to patients

Valproate can seriously harm an unborn child when taken during pregnancy. Therefore:

- Reliable contraception should be used and maintained throughout treatment with valproate
- Tell the doctor if they want to have a baby before contraceptive use is discontinued
- Report to the doctor immediately if they suspect or know they are pregnant
- Do not stop taking valproate unless advised by their doctor.

The MHRA has produced a valproate [patient card](#) and [guide](#) to be given to all patients of child bearing potential. This guide will be issued by the prescriber and the card with the dispensed medication. Patients should be advised to read the information contained and to keep it as a reminder.

## 4. Prescriber's responsibilities

- Prescribing valproate must be started and supervised by a specialist experienced in the indication for which it is being used
- Valproate should not be prescribed to females of child bearing potential unless other treatments are ineffective or not tolerated and the benefits of treatment are assessed as higher than the risks involved.
- Carefully balance the benefits of valproate treatment against the risks when prescribing valproate for the first time, at routine treatment reviews, when a female child reaches puberty and when a woman plans or becomes pregnant.
- Prescribers must ensure that they are aware of the risks of using valproate in women of childbearing potential and during pregnancy and what steps to consider. The [healthcare professional booklet](#) is a useful resource.
- Provide the patient with information about valproate and the risks of use (regardless of the indication); and give those of child bearing potential, a copy of the [Valproate Patient Guide](#)

- A consultation [checklist](#) for prescribers has been developed by the MHRA as a guide to the discussion that needs to be had with the female patient. This must be ticked off as appropriate and signed by *both* the prescriber and the patient and then scanned into the patient's notes as a permanent record of the discussion.
- The above document also serves as the patient consent to treatment with valproate
- Discuss and ensure adequate contraception use in women of childbearing potential and document that this has been done.
- Offer folic acid supplements to patients at risk of becoming pregnant while on valproate
- Regularly review treatment and refer when appropriate
- Report any adverse effects including those suspected in a baby or child who was exposed to valproate in utero, via the Yellow Card scheme <https://yellowcard.mhra.gov.uk>.

## 5. General prescribing advice for the treatment of bipolar disorder

- Before starting valproate, baseline full blood count, including liver function test and urea and electrolytes and body weight are recommended. Valproate is hepatically metabolised, and can cause thrombocytopenia, hyponatraemia and weight gain.
- Do not stop valproate abruptly – except in cases of toxicity. Reduce slowly over at least one month to stop.
- Prescribe sodium valproate (in preference to the semi-sodium valproate) wherever possible.
- The form of valproate prescribed should always be clearly stated. Immediate release, enteric coated (e/c) valproate preparations are usually recommended first line e.g. *Sodium valproate E/C 200mg OM, 400mg ON*.
- Modified or controlled release (mr/cr/ chrono) preparations of sodium valproate are an option if the e/c is not tolerated (the m/r tend to be better tolerated as they do not cause peak levels as high as the conventional formulations). For epilim<sup>®</sup>, the EC is sodium valproate while the chrono is a mix of sodium valproate and valproic acid.
- The modified release preparations can also be given as a single daily dose. All other formulations must be given at least twice daily
- In acute mania, doses of 20-30mg/kg or a total daily dose between 1000mg-2000mg (for adults) may be used. Rapid dose escalations are generally well tolerated.

## 6. Role of pharmacy/dispensary

- Issue a valproate [card](#) with all dispensed valproate for women of child bearing potential
- Give a patient information leaflet with all dispensed valproate for leave, discharge or outpatient prescriptions

## 7. References and further reading

- Maudsley Prescribing Guidelines 12<sup>th</sup> edition
- MHRA letter (February 2016) Valproate and risk of abnormal pregnancy outcomes: new communication materials
- NICE Guidelines [CG185](#) – Bipolar disorder assessment and management
- Oxford Health NHS Foundation Trust MI bulletin vol.14 No. 1 – Valproate for bipolar disorder – formulary status reminder
- Psychotropic drug directory 2014
- Sussex Partnership NHSFT Guidance on prescribing valproate in women of childbearing potential
- Summary of product characteristics [www.medicines.org.uk](http://www.medicines.org.uk)
- UK Teratology Information Service monograph on Valproate [www.uktis.org](http://www.uktis.org)
- European Commission decision on Valproate August 2010  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Valproate/human\\_referral\\_000187.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Valproate/human_referral_000187.jsp)

Version history				
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