

# Drug Safety Update



## Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

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The Medicines and Healthcare products Regulatory Agency is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.



The MHRA is accredited by NICE to provide Drug Safety Update. Further information can be found on the NICE Evidence Search portal: [www.evidence.nhs.uk/](http://www.evidence.nhs.uk/)

In January 2015 [we informed you](#) that children exposed to valproate in utero are at high risk of developmental disorders and congenital malformations. To further improve awareness of the risks of valproate in pregnancy we are asking that you use new communication materials to support discussion of these risks with women of childbearing potential and girls who take valproate—see page 2.

We would also like to remind you that concomitant use of spironolactone for congestive heart failure with an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker (ARB) is not routinely recommended because of the risks of severe hyperkalaemia, particularly in patients with marked renal impairment. Use the lowest effective doses if coadministration of these medicines is considered essential and monitor blood electrolytes—see page 4.

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## 1 Valproate and of risk of abnormal pregnancy outcomes: new communication materials

In January 2015 [we informed you](#) that children exposed to valproate in utero are at high risk of developmental disorders and congenital malformations. To further improve awareness of the risks of valproate in pregnancy we are asking that you use the new communication materials below to support discussion of these risks with women of childbearing potential and girls who take valproate. Hard copies are being sent to relevant healthcare professionals from this week.

### Resources to use (see below for more information):

- [Booklet for Healthcare Professionals](#)
- Consultation [checklist](#)
- [Guide](#) to give to patients
- [Card](#) to give to patients

Later in 2016, the outer packaging for medicines containing valproate will include a warning for women on the risk of adverse pregnancy outcomes.

### Summary of risks and precautions

1. Meador K et al. [Lancet Neurol](#) 2013;12(3):244-52
2. Christensen J et al. [JAMA](#) 2013;309(16):1696-703
3. Veiby G et al. [Epilepsia](#) 2013;54(8):1462-72.
4. Cohen MJ et al. [Epilepsy Behav](#) 2013;29(2):308-15
5. Bromley RL et al. [Epilepsia](#) 2010;51(10):2058-65.
6. Cummings et al. [Arch Dis Child](#) 2011;96(7):643-7
7. Meador K et al. [NEJM](#) 2009;360(16):1597-605
8. Thomas S.V et al. [Epilepsy Behav](#) 2008;13(1):229-36
9. Bromley R et al. [Cochrane Database of Systematic Reviews](#) 2014, Issue 10

- Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and congenital malformations (in approximately 10% of cases)<sup>1-9</sup>
- Valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated.
- Valproate treatment must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder.
- 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 a pregnancy or becomes pregnant.
- You must ensure that all female patients are informed of and understand:
  - the risks associated with valproate during pregnancy;
  - the need to use effective contraception;
  - the need for regular review of treatment;
  - the need to rapidly consult if she is planning a pregnancy or becomes pregnant

### For specialists (neurologists, psychiatrists and paediatricians)

We are asking that you use the following communication materials to help manage and minimise the risks outlined above. If you manage specialist care in your organisation, ensure that processes are in place to allow these requirements to be met.

#### *Healthcare professional booklet*

Read the [healthcare professional booklet](#) which gives:

- a comprehensive overview of the risks of valproate in females of childbearing potential and during pregnancy,
- points to consider and steps to take when deciding to treat women of childbearing potential and girls with valproate.

#### *Consultation checklist*

Whenever you conclude it necessary to treat or continue treating a woman of childbearing potential or girl with valproate, use the [checklist](#) to check that you have given her all the necessary information and that she has fully understood it. Add the completed checklist to her medical records as a permanent record of your discussion.

## Patient guide

When considering treating a woman of childbearing potential or girl with valproate, give her or her carer the valproate [patient guide](#) and ensure that she understands the information it contains.

Paediatricians should also refer parents or carers to the [information about valproate from the Royal College of Paediatrics and Child Health](#).

## For pharmacists

- Whenever you dispense a medicine related to valproate for a woman of childbearing potential or girl, give her a [patient card](#), unless she confirms that she already has one.
- Encourage her to read the card (example in figures below) and enter her name and date to reinforce her own accountability to consider the information it contains.
- If you manage dispensing services in your organisation, ensure that processes are in place to allow these requirements to be met.
- Please continue to report any suspected side effects to valproate or any other medicine on a [Yellow Card](#) (see also [guidance on reporting side effects experienced by the woman or child to medicines taken during pregnancy](#)).

## For general practitioners:

- Valproate treatment must be started and supervised by a specialist experienced in managing epilepsy or bipolar disorder.
- Consider the need to arrange treatment reviews with the relevant specialist for women of childbearing potential and girls who are currently taking valproate.
- If a woman who is taking valproate tells you she is pregnant or would like to have a baby, refer her to the specialist responsible for her care.
- Please continue to report any suspected side effects to valproate or any other medicine on a [Yellow Card](#) (see also [guidance on reporting side effects experienced by the woman or child to medicines taken during pregnancy](#)).

## Further information:

Valproate healthcare professional booklet:  
[www.medicines.org.uk/emc/RMM.420.pdf](http://www.medicines.org.uk/emc/RMM.420.pdf)

Valproate consultation checklist:  
[www.medicines.org.uk/emc/RMM.423.pdf](http://www.medicines.org.uk/emc/RMM.423.pdf)

Valproate patient guide:  
[www.medicines.org.uk/emc/RMM.421.pdf](http://www.medicines.org.uk/emc/RMM.421.pdf)

Valproate patient card:  
[www.medicines.org.uk/emc/RMM.422.pdf](http://www.medicines.org.uk/emc/RMM.422.pdf)

[Summaries of product characteristics](#)

[Letter sent to healthcare professionals](#) in Feb 2015

Drug Safety Update articles on valproate from [November 2013](#) and [January 2015](#)

[Further information from the MHRA](#)

[Epilepsy Action statement](#) 8 February 2016

[NICE Guidance for bipolar disorder](#) September 2014

[NICE Guidelines for epilepsy](#) January 2012

## Off-label use: risks and advice still apply

Valproate is not licensed for treatment of conditions other than epilepsy or bipolar disorder in the UK. However, we are aware that these medicines are sometimes used 'off-label' (eg for migraine or chronic pain). If you are considering initiating or continuing such treatment, the same risks and advice in this article apply.

## Monitoring effectiveness of risk minimisation

The effectiveness of the above risk minimisation measures will be continuously monitored via prescribing data and evaluation of levels of patient awareness. Results will be communicated as they become available. As with all medicines, we will continue to monitor the safety and efficacy of valproate to assess the need for further regulatory action.

**Key Facts – Valproate and Pregnancy**

Name:  Date:

- Valproate is an effective medicine used to treat epilepsy and bipolar disorder.
- Valproate can seriously harm an unborn child when taken during pregnancy and should be not taken by women and girls unless nothing else works.
- When taking valproate always use reliable contraception so you do not have an unplanned pregnancy.

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) for how to report side effects.

**What you must do**

- Speak to your doctor if you are thinking about having a baby, and do not stop using contraception until you have done so.
- Tell your doctor at once if you think you may be pregnant or know you are pregnant.
- Never stop taking valproate unless your doctor tells you to as your condition may become worse.

Keep this card safe so you always know what to do.

SAGB.VPA.15.12.1440b January 2016

Figure: front and back of patient card

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## 2 Spironolactone and renin-angiotensin system drugs in heart failure: risk of potentially fatal hyperkalaemia

Monitoring of blood electrolytes is essential in patients coprescribed a potassium-sparing diuretic and an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) for heart failure.

### Reminder for healthcare professionals:

- Concomitant use of spironolactone with ACEi or ARB is not routinely recommended because of the risks of severe hyperkalaemia, particularly in patients with marked renal impairment
- Use the lowest effective doses of spironolactone and ACEi or ARB if coadministration is considered essential
- Regularly monitor serum potassium levels and renal function
- Interrupt or discontinue treatment in the event of hyperkalaemia
- Suspected adverse reactions should be reported to us on a [Yellow Card](#)

### Risk of hyperkalaemia with spironolactone

Spironolactone is indicated in patients with congestive heart failure. It is a competitive aldosterone antagonist that increases sodium excretion while reducing potassium loss at the distal renal tubule. This mechanism of action means that hyperkalaemia can occur, particularly in patients with impaired renal function. Spironolactone should not be used in patients with severe renal impairment or pre-existing hyperkalaemia.

### Risk of hyperkalaemia with renin-angiotensin system drugs

ACEi are mainly indicated in patients with hypertension or heart failure. ARBs are also indicated in hypertension and some are also indicated in heart failure. Recognised side effects of treatment with an ACEi or ARB include renal dysfunction and an increase in serum potassium. Risk factors for hyperkalaemia, such as renal insufficiency and diabetes mellitus, are more common in patients who require treatment with ACEi or ARB. Dehydration may also increase the risk of renal dysfunction leading to hyperkalaemia. Hyperkalaemia has been estimated to occur in between 1 in 100 and 1 in 1000 patients who take an ACEi or ARB.

### Reporting of cases of hyperkalaemia

A recent coroner's case reported to us described a case of fatal hyperkalaemia in a patient with heart failure, diabetes, and chronic renal failure who was being treated with several medicines including spironolactone. A low-dose ACEi was subsequently added for treatment of increased blood pressure. A few days later, the patient was admitted to hospital with severe hyperkalaemia and acute-on-chronic renal failure and subsequently died.

Between January 1998 and December 2015, we have received 82 UK spontaneous reports of abnormal blood potassium in patients using spironolactone as well as an ACEi (n=63) or ARB (n=25), 70 of which describe hyperkalaemia. 3 patients taking spironolactone and ACEi had a fatal outcome.

The number of cases reported for concomitant use of spironolactone and ACEi has increased from 1999, peaking 2001–05, and has started rising again in the past 2 years (see figure). During the period from 1982 (when the first report of hyperkalaemia with this combination of medicines was received) to 1998, only 7 cases of hyperkalaemia with spironolactone and an ACEi or ARB were reported.

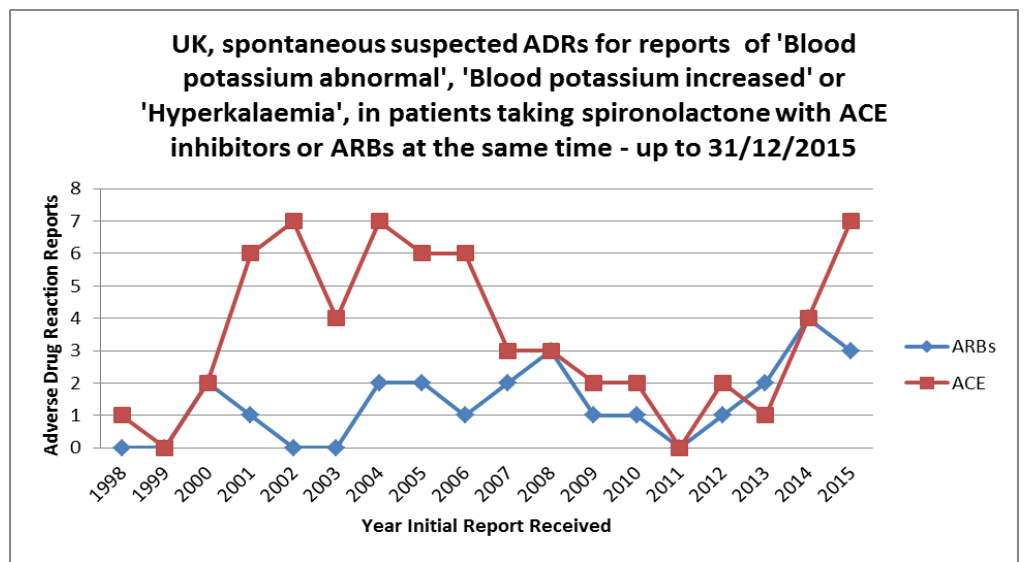


Figure: Reported UK spontaneous cases of abnormal or increased blood potassium, or hyperkalaemia, in patients using spironolactone and ACEi (63) or ARB (25) at the same time for the period January 1998 to December 2015. Note: some cases included both ACEi and ARB use with spironolactone.

1. Pitt B, et al. [The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators.](#) N Engl J Med 1999; 341: 709–17.
2. Juurlink D, et al. [Rates of hyperkalemia after publication of the randomized aldactone evaluation study.](#) N Engl J Med 2004; 351: 543–51.

In 1999, the Randomised Aldactone Evaluation Study (RALES)<sup>1</sup> reported a relative risk reduction in death for patients treated with spironolactone compared with placebo, in addition to standard therapy (including ACEi) if tolerated. The incidence of hyperkalaemia in RALES was low. In 2004, a study in the USA and Canada found an association between spironolactone use and hyperkalaemia-associated morbidity and mortality in patients treated with ACEi who had been recently admitted to hospital for heart failure.<sup>2</sup> This observation was thought to be due to differences between conditions and baseline patient characteristics in the RALES trial compared with those seen in routine clinical practice.<sup>2</sup> The peak of UK reporting after 1999 possibly reflects increased use of spironolactone and ACEi following RALES.

The recent increase in reporting has coincided with the outcome of a European review on dual blockade therapy with ACEi and ARB. [This review concluded](#) that combination use of ACEi and ARB (which both inhibit the renin-angiotensin system) is not recommended because of an increased risk of hyperkalaemia, hypotension, and impaired renal function. The recent increase in number of UK cases reported could reflect an increase in coadministration of spironolactone and ACEi or ARB, or it could represent stimulated reporting due to increased awareness of the risks.

*Article citation: Drug Safety Update volume 9 issue 6 February 2016: 2.*

### 3 Letters sent to healthcare professionals in January 2016

In January 2016, letters were sent to healthcare professionals to notify about safety information for:

- Fingolimod ([Gilenya ▼](#)): risks related to effects on the immune system
- Erlotinib ([Tarceva](#)): first-line maintenance indication now restricted to patients with a tumour that has an EGFR-activating mutation

*Article citation: Drug Safety Update volume 9 issue 6 February 2016: 3.*