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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Contents

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.

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This month read about the new European review to examine the use of valproate-containing medicines (Epilim▼, Depakote▼) in women and girls (page 2). We also provide information about the new Patient Safety Alerts to support the safe prescribing and dispensing of valproate medicines. Organisations should identify and review all women and girls taking valproate medicines and arrange a review of medication and contraception.

In addition, read the updated dose advice for ponatinib (Iclusig▼) treatment (page 4). You should consider reducing the dose of ponatinib in patients with chronic phase chronic myeloid leukaemia (CP-CML) who have achieved a major cytogenetic response while on treatment. Review the product information and take individual patient factors into account when considering dose reductions in these patients.

Also this month, we have an article relating to reports about a safety signal with fingolimod (Gilenya▼) and other treatments for multiple sclerosis. See page 5 for further information on how you can help us to evaluate the risk.

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Valproate and developmental disorders: new alert asking for patient review and further consideration of risk minimisation measures

Babies born to mothers who take valproate medicines (Epilim▼, Depakote▼) during pregnancy have a 30–40% risk of developmental disability and a 10% risk of birth defects. Despite communications to prescribers in January 2015 and February 2016 on the magnitude of this risk and the actions to take, there is evidence that women are still not aware of the risk. Patient Safety Alerts have now been issued asking all organisations to undertake systematic identification of women and girls taking valproate. A new European review is considering whether further regulatory action is necessary and there will be a public hearing at the European Medicines Agency later in 2017.

Advice for healthcare professionals:

- do not prescribe valproate medicines for epilepsy or bipolar disorder in women and girls unless other treatments are ineffective or not tolerated; migraine is not a licensed indication
- ensure women and girls taking valproate medicines understand the 30–40% risk of neurodevelopmental disorders and 10% risk of birth defects and are using effective contraception
- valproate use in women and girls of childbearing potential must be initiated and supervised by specialists in the treatment of epilepsy or bipolar disorder

Risks of exposure in pregnancy and previous communications

Babies exposed to valproate-containing medicines (Epilim▼, Depakote▼) in utero are at very high risk of developmental disorders and congenital malformations. After warnings were strengthened at the European level, in 2015 we advised you against prescribing valproate-containing medicines in girls and women of or nearing childbearing potential unless other treatments are ineffective or not tolerated.

In 2016 we released further communication materials and resources to support discussion of these risks with women and girls of childbearing potential who take valproate.

The MHRA's toolkit resources have been disseminated widely. However, evidence suggests as many as 1 in 5 women taking valproate are not aware of any of its risks in pregnancy. Evidence from the Clinical Practice Research Datalink also suggests that, although prescription rates for valproate have been declining gradually in recent years, the measures put in place have not had a significant effect.

New Patient Safety Alerts

On 6 April 2017, NHS Improvement and MHRA sent a Patient Safety Alert through the NHS Central Alerting System to further highlight risks to the unborn child and support the safety of girls and women taking valproate. Consistent action is being taken in Scotland, Wales, and Northern Ireland.

These alerts direct organisations to undertake systematic identification of women and girls taking valproate and to use the MHRA resources to support them to make informed choices.

Further European review

In March 2017, the European Pharmacovigilance Risk Assessment Committee (PRAC) initiated a further review to look at the use of valproate-containing medicines in women and girls of childbearing potential. The committee will consider whether these medicines require further restrictions of use due to their very high risk of causing developmental disorders and congenital malformations to unborn babies and evidence of continued use in pregnancy. The review will also examine the effectiveness of regulatory measures put in place to increase awareness and reduce valproate use in patients at risk.

The European Medicines Agency has decided to organise a public hearing later this year as part of their review of valproate. The hearing will be announced prominently on the European Medicines Agency's website together with a list of specific questions on which information from the public is sought and information on the date, time, location, and how to register.

We will tell you about the results of the review of the use of valproate-containing medicines when they are announced.

Further information

Patient Safety Alert—Resources to support the safety of girls and women who are being treated with valproate (6 April 2017)
MHRA valproate toolkit
Template letter for GPs to invite in patients
Booklet for Healthcare Professionals
Guidance for those prescribing and dispensing valproate
Consultation checklist for patients and prescribers
Guide to give to patients in English and in Welsh
Card to give to patients in English and in Welsh
Summaries of product characteristics for valproate medicines
Drug Safety Update articles on valproate medicines from November 2013, January 2015, and February 2016
NICE Guidance for bipolar disorder (July 2015)
NICE Guidance for epilepsy (February 2016)

Article citation: Drug Safety Update volume 10 issue 9, April 2017: 1.

Ponatinib (Iclusig▼): risk of vascular occlusive events—updated advice on possible dose reduction

Prescribers should consider reducing the dose of ponatinib to 15 mg a day for patients with chronic phase chronic myeloid leukaemia (CP-CML) who have achieved a major cytogenetic response.

Background

Ponatinib (Iclusig▼) is a treatment for adults with chronic myeloid leukaemia or Philadelphia-chromosome-positive acute lymphoblastic leukaemia. Its authorised use is restricted to patients who have limited alternative treatment options with tyrosine kinase inhibitors. For full information on the authorised indication, see the summary of product characteristics.

Updated data

In November 2014, we informed you about the conclusions of a European-level review of the risk of serious vascular occlusive events with ponatinib and highlighted advice on risk minimisation. Additional long-term follow-up data are now available that provide further information and support new advice on dose modifications to reduce this risk.

The available evidence shows that the risk of arterial occlusion with ponatinib is likely to be dose-dependent and that dose reduction may therefore reduce the risk of life-threatening vascular events. The additional data from long-term follow-up of clinical trial patients with chronic phase chronic myeloid leukaemia (CP-CML) who have undergone dose reduction after achieving a major cytogenetic response provide reassurance that ponatinib continues to be effective in maintaining this response when a lower dose is taken.

Dose advice

The recommended starting dose of ponatinib remains at 45 mg once a day for all patients.

Prescribers should consider reducing the dose of ponatinib to 15 mg a day for patients with CP-CML who have achieved a major cytogenetic response while on treatment.

The following factors should be taken into account in the individual patient assessment:

- cardiovascular risk
- side effects of ponatinib therapy (including cardiovascular and other dose-related toxicity)
- time to cytogenetic response
- BCR-ABL transcript levels

If dose reduction is undertaken, close monitoring of response is recommended.

Please continue to report any suspected adverse reactions via the Yellow Card Scheme.

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Multiple sclerosis therapies: signal of rebound effect after stopping or switching therapy

Healthcare professionals should report any suspected adverse effects relating to fingolimod (Gilenya▼) or other treatments for multiple sclerosis, including suspected adverse effects occurring after discontinuation, via the Yellow Card Scheme.

We are aware of two recently published articles[1,2] describing a suspected rebound syndrome (clinical and radiological signs of severe exacerbation beyond what was expected for that patient prior to discontinuation or treatment change) in patients with multiple sclerosis after treatment with fingolimod (Gilenya▼) was stopped, some of whom were switched to other treatments.

In conjunction with other European national regulatory authorities and the European Medicines Agency, we are evaluating all available evidence on this safety signal. Further information on the outcome of the review and any relevant new guidance will be issued as soon as it is available.

Healthcare professionals are reminded to be vigilant for such events and report any suspected adverse effects relating to fingolimod or other treatments for multiple sclerosis via the Yellow Card Scheme.

For any reports of suspected rebound effect, please provide as much detail as possible. This could include any clinical, imaging and other test details; along with a description of disease activity prior to and during therapy.

Article citation: Drug Safety Update volume 10, issue 9, April 2017: 3

1 Hatcher SE et al. Rebound syndrome in patients with multiple sclerosis after cessation of fingolimod treatment. JAMA Neurol 2016; 73: 790–94.

2 Willis M et al. An observational study of alemtuzumab following fingolimod for multiple sclerosis. Neurol Neuroimmunol Neuroinflamm 2017; 4: e320.

Letters sent to healthcare professionals in March 2017

In March 2017, the following letter was sent to relevant healthcare professionals to inform them of updated safety information:

- Nulojix (belatacept) 250 mg: supply shortage—restricted to existing patients

We are also aware of the following letter, which was sent to relevant healthcare professionals in October 2016:

- Mucodyne Paediatric Syrup 250 mg/5 mL (carbocisteine oral liquid): new double-strength presentation—check dose volume to ensure appropriate dose is given

Article citation: Drug Safety Update volume 10, issue 9, April 2017: 4.