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, we inform you of important new information and strengthened warnings related to safety of medicines related to valproate (sodium valproate, valproic acid [brand leader: Epilim] and valproate semisodium [brand leader: Depakote]), following completion of a Europe-wide review. Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and/or congenital malformations (in approximately 10% of cases)—see article 1.

We have received reports of exfoliative dermatitis in patients being treated with ustekinumab for plaque psoriasis. If you suspect exfoliative dermatitis caused by an adverse drug reaction to ustekinumab, stop treatment. Be alert to signs of exfoliative dermatitis in patients receiving ustekinumab and tell patients to report relevant symptoms—see article 2.

Mycophenolate mofetil in combination with other immunosuppressants can cause persistent hypogammaglobulinaemia associated with recurrent infections. Measure serum immunoglobulins in patients who develop recurrent infections. Mycophenolate mofetil can also cause bronchiectasis and pulmonary fibrosis. Consider these diagnoses if patients develop persistent pulmonary symptoms, such as cough and dyspnoea. In some cases, switching from mycophenolate mofetil to another immunosuppressant has improved these conditions. These recommendations also apply to medicines that contain mycophenolic acid as their active ingredient—see article 3.

Oral diclofenac can no longer be sold to anyone without a prescription. Diclofenac is associated with a small risk of cardiovascular side effects (eg myocardial infarction, stroke). Therefore patients should have a medical assessment before taking diclofenac to determine if it is suitable for them—see article 4.

The treatment advice for aceclofenac has been updated in line with diclofenac and COX-2 inhibitors. Aceclofenac is now contraindicated in patients with certain established heart conditions—see article 5.
Finally, we have simplified our medicine and device incident report systems by bringing them all under the Yellow Card Scheme. Please report any of the following on a Yellow Card: suspected adverse drug reactions, medical device incidents, defective medicines, and counterfeit medicines—see article 6.

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1 Medicines related to valproate: risk of abnormal pregnancy outcomes

Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and/or congenital malformations (in approximately 10% of cases).

This is to inform you of important new information and strengthened warnings related to safety of medicines related to valproate (sodium valproate, valproic acid [brand leader: Epilim] and valproate semisodium [brand leader: Depakote]), following completion of a Europe-wide review:

- children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and/or congenital malformations (in approximately 10% of cases)
- 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:
    - risks associated with valproate during pregnancy
    - need to use effective contraception
    - need for regular review of treatment
    - the need to rapidly consult if she is planning a pregnancy or becomes pregnant

Please refer to the General Medical Council's consent and prescribing guidance.

Risk of abnormal pregnancy outcomes

Valproate is associated with a dose-dependent risk of abnormal pregnancy outcomes, whether taken alone or in combination with other medicines. Data suggest that when valproate is taken for epilepsy with other medicines, the risk of abnormal pregnancy outcomes is greater than when valproate is taken alone.

The risk of congenital malformations is approximately 10 % while studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking, and/or walking, have low intellectual abilities, poor language skills and memory problems.[1-5]

Intelligence quotient (IQ) measured in a study of 6 years old children with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics.[6]

Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).[7-9]

Given these risks, valproate for the treatment of epilepsy or bipolar disorder should not be used during pregnancy and in women of child-bearing potential unless clearly necessary ie in situations where other treatments are ineffective or not tolerated.

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.

1. Meador K et al. Epilepsy Res. 2008;81(1):1-13.
2. Meador K et al. Epilepsy Behav. 2009;15(3):339-43.
3. Bromley R et al. Neurology. 2008;71(23):1923-4.
4. Thomas S et al. Epilepsia. 2007 Dec;48(12):2234-40.
5. Cummings C et al. Arch Dis Child 2011 July;96(7):643-7.

6. Meador K et al. Lancet Neurol. 2013;12(3):244-52.

7. Christensen J et al. JAMA. 2013; 309(16):1696-703.
8. Cohen M et al. Epilepsy Behav. 2013;29(2):308-15.
9. Cohen M et al. Epilepsy Behav. 2011; 22(2):240-246

If you decide to prescribe valproate to a woman of child-bearing potential, she must use effective contraception during treatment and be fully informed of the risks for the unborn child if she becomes pregnant during treatment with valproate.

Treatment during pregnancy
If a woman with epilepsy or bipolar disorder who is treated with valproate plans a pregnancy or becomes pregnant, consideration should be given to alternative treatments.
If valproate treatment is continued during the pregnancy:

- the lowest effective dose should be used and the daily dose should be divided into several small doses to be taken throughout the day - the use of a prolonged release formulation may be preferable to other treatment forms
- initiate specialised prenatal monitoring in order to monitor the development of the unborn, including the possible occurrence of neural tube defects and other malformations
- folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies; however the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure

Further information
The Cochrane review[10] published in November 2014 assessed 22 prospective cohort studies and 6 registry studies. The review supported findings from the European review that children exposed to valproate in utero were at an increased risk of poorer neurodevelopmental scores compared to the general study population both in infancy and when school aged.

A dose-related risk of developmental disorders was reported for valproate in 6 of the 28 studies included in the Cochrane review. However, based on the available data, it is not possible to establish a threshold dose below which no risk of developmental disorders exists.

Usage during pregnancy in the UK
Data from the Clinical Practice Research Datalink suggest that approximately 35,000 women aged 14 to 45 per year had a prescription for sodium valproate between 2010 and 2012, the majority for epilepsy. Of these, at least 375 per year had a prescription for sodium valproate while pregnant.

Future action
Pharmaceutical companies holding licences for valproate containing medicines must monitor the usage of these medicines to assess the effectiveness of these new measures on reducing the number of pregnant women taking valproate. We will continue to monitor valproate usage using the Clinical Practice Research Datalink. We will also work with stakeholders such as clinical guideline bodies to develop tools to aid decision-making for healthcare professionals and patients. We have already developed information booklets for healthcare professionals and patients (see further information below).

The product information will now be updated to reflect our current understanding of the available evidence and to make information as clear as possible.

Educational materials are available to healthcare professionals and patients in order to inform about the risks associated with valproate in female children, female adolescents, women of childbearing potential and pregnant women (see further materials below).

Call for reporting
Valproate is now a black triangle medicine and is subject to additional monitoring. Therefore please report any suspected side effects to valproate via the Yellow Card scheme www.gov.uk/yellowcard.

Article citation: Drug Safety Update volume 8 issue 6 January 2015: 1

10. Bromley R, Weston J, Adab N et al. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. Cochrane Database Syst Rev. 2014, Issue 10

Further information
Guide for healthcare professionals Jan 2015
Valproate booklet for patients Jan 2015
Summaries of product characteristics and patient information leaflets
Letter sent to healthcare professionals 21 Jan 2015
Information from the European Medicines Agency Nov 2014

2 Ustekinumab (Stelara): risk of exfoliative dermatitis

If you suspect exfoliative dermatitis caused by an adverse drug reaction to ustekinumab, stop treatment.

When using ustekinumab to treat plaque psoriasis or active psoriatic arthritis:

- be alert for signs and symptoms of exfoliative dermatitis or erythrodermic psoriasis
- start appropriate treatment promptly if a patient develops widespread erythema and skin exfoliation
- stop ustekinumab treatment if you suspect exfoliative dermatitis caused by an adverse drug reaction to ustekinumab
- tell patients to report symptoms of exfoliative dermatitis or erythrodermic psoriasis (eg increased redness and shedding of skin over a larger area of the body) to their doctor promptly
- please continue to report suspected adverse drug reactions to ustekinumab or any other medicines on a Yellow Cardwww.gov.uk/yellowcard

Ustekinumab (Stelara) is licensed to treat moderate to severe plaque psoriasis and active psoriatic arthritis in adults for whom other non-biological systemic therapies have not worked. Full prescribing information can be found in the summary of product characteristics.

Exfoliative dermatitis

We have received rare Yellow Card reports of exfoliative dermatitis in patients being treated with ustekinumab for plaque psoriasis. Symptoms reported included widespread erythema, scaling, itching, and skin exfoliation. In some cases skin exfoliation occurred without other symptoms of exfoliative dermatitis. In many cases patients were hospitalised as a result of the symptoms.

In some cases symptoms started within a week of the first dose, suggesting a possible link to ustekinumab.

Symptoms of exfoliative dermatitis may be very similar to those of erythrodermic psoriasis. Erythrodermic psoriasis may develop as part of the natural course of plaque psoriasis. Consider both exfoliative dermatitis and erythrodermic psoriasis as possible causes if symptoms occur in a patient receiving ustekinumab.

Further information
Letters to healthcare professionals sent in November 2014

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3 Mycophenolate mofetil (CellCept) and mycophenolic acid: risk of hypogammaglobulinaemia and risk of bronchiectasis

Measure serum immunoglobulin levels if recurrent infections develop. Consider bronchiectasis or pulmonary fibrosis if patients develop persistent respiratory symptoms.

When using mycophenolate mofetil or any other medicine containing mycophenolic acid (MPA) as its active ingredient:

- measure serum immunoglobulin levels if recurrent infections develop
- in cases of sustained, clinically relevant hypogammaglobulinaemia, consider appropriate clinical action. Take into account the potent cytostatic effects of MPA on B-lymphocytes and T-lymphocytes
- consider bronchiectasis or pulmonary fibrosis if patients develop persistent respiratory symptoms, such as cough and dyspnoea
- please continue to report suspected adverse drug reactions to mycophenolate mofetil, medicines containing MPA, or any other medicines on a Yellow Card www.gov.uk/yellowcard

Mycophenolate mofetil (brand leader: CellCept) is licensed in combination with ciclosporin and corticosteroids to prevent acute transplant rejection in patients receiving allogeneic renal, cardiac, or hepatic transplants. It is also used off-label in other specialties, such as rheumatology, gastroenterology, respiratory medicine, and dermatology.

Mycophenolate mofetil is a prodrug that is completely converted to the active pharmacological form mycophenolic acid (MPA). MPA has potent cytostatic effects on both B-lymphocytes and T-lymphocytes.

Hypogammaglobulinaemia

A review by European regulators concluded that mycophenolate mofetil in combination with other immunosuppressants can cause hypogammaglobulinaemia in adults and children, which can be associated with recurrent infections. This conclusion was based on published reports,[1-2] clinical trial data, and reports from clinical practice. Switching from mycophenolate mofetil to an alternative immunosuppressant resulted in serum immunoglobulin G (IgG) levels returning to normal in some cases.

Bronchiectasis

The review also concluded that mycophenolate mofetil in combination with other immunosuppressants can cause bronchiectasis in adults and children (sometimes years after starting mycophenolate mofetil treatment). The risk of bronchiectasis may be linked to hypogammaglobulinaemia or to a direct effect of MPA on the lungs. Patients who developed bronchiectasis usually presented with a persistent productive cough and, in some cases, recurrent upper or lower respiratory tract infections.[3-5] The diagnosis was confirmed by high resolution computed tomography of the chest. In some of these cases, switching from mycophenolate mofetil to another immunosuppressant improved respiratory symptoms. Mycophenolate mofetil is also known to cause pulmonary fibrosis.

To date, we have received 13 Yellow Card reports* of hypogammaglobulinaemia and 12 Yellow Card reports[6] of bronchiectasis associated with mycophenolate use. Bronchiectasis can occur after years of mycophenolate mofetil treatment, so the link to mycophenolate mofetil may not be made.

1. Keven K et al. Transpl Infect Dis 2003;5:181-6.
2. Robertson J et al. Pediatr Transplant 2009;13:754-9.
3. Boddana P et al. Clin Transplant 2011; 25:417-9.
4. Pijnenburg MW et al. Pediatr Transplant 2004;8:71-4.
5. Rook M et al. Transplantation 2006;81:287.

Further information

Mycophenolate mofetil summary of product characteristics

*Yellow Card reports are reports of suspected adverse drug reactions (ADRs) taken from all spontaneous and study sources. Spontaneous reports are those submitted voluntarily by healthcare professionals and members of the public in the UK. The number of reports received should not be used to determine the incidence of an ADR. This is because neither the total number of ADRs occurring, nor the number of patients using the drug is known. ADR reporting rates are influenced by the seriousness of ADRs, their ease of recognition, and the extent of use of a particular drug, and may be stimulated by publicity about a drug.

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4 Oral diclofenac no longer available without prescription

Oral diclofenac is associated with a small increased risk of cardiovascular side effects and is therefore no longer available over the counter.

When prescribing or dispensing diclofenac, consider that:

- oral diclofenac must not be sold without prescription
- a recall has been issued for non-prescription diclofenac
- the prescribing advice for diclofenac was updated in June 2013
- topical formulations of diclofenac (eg gel and cream) remain available for sale over the counter

Advice to give to patients:

- if you have recently bought diclofenac tablets without a prescription and continue to need pain relief, speak to your prescriber or pharmacist who can advise you on suitable alternatives - there is no problem if you wish to stop taking diclofenac in the meantime
- if you have been prescribed diclofenac there is no need to stop taking the medicine - speak to your prescriber or pharmacist at your next routine visit if you have any heart problems or other concerns about the treatment

Diclofenac is a non-steroidal anti-inflammatory drug used to treat pain and inflammation. Diclofenac tablets must no longer be sold to anyone without a prescription. Diclofenac is associated with a small risk of serious cardiovascular side effects (eg myocardial infarction and stroke). Therefore patients should have a medical assessment before taking diclofenac to determine if it is suitable for them.

Further information
Drug Alert 14 Jan 2015
Information to give to patients
MHRA press release 14 Jan 2015

Reporting side effects
Please report any suspected side effects to any medicine or vaccine to the Yellow Card Scheme www.gov.uk/yellowcard. By reporting side effects you can help provide more information on the safety of medicines.

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5 Aceclofenac (Preservex): updated cardiovascular advice in line with diclofenac and COX-2 inhibitors

Aceclofenac is now contraindicated in patients with certain established cardiovascular diseases.

When using aceclofenac to relieve pain and inflammation in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, you should:

- consider that aceclofenac is now contraindicated in patients with established:
  - ischaemic heart disease
  - peripheral arterial disease
  - cerebrovascular disease
  - congestive heart failure (New York Heart Association, NYHA, classification II-IV)
- switch patients with these conditions to an alternative treatment at their next routine appointment
- only start aceclofenac treatment after careful consideration of any significant risk factors for cardiovascular events, eg
  - hypertension
  - hyperlipidaemia
  - diabetes mellitus
  - smoking

Aceclofenac (Preservex) is a non-steroidal anti-inflammatory drug (NSAID) licensed for

the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Aceclofenac has little pharmacological activity itself; its main mode of action is through its metabolites which include diclofenac and 4'-hydroxy diclofenac.

In June 2013 we told you about the new contraindications and warnings for diclofenac. This was after a review by European regulators concluded that the risk of arterial thrombotic events (myocardial infarction; stroke) with diclofenac is greater than with other non-selective NSAIDs and similar to the COX-2 inhibitors.

There are limited data available regarding the arterial thrombotic effects of aceclofenac. The treatment advice for aceclofenac has been updated in line with diclofenac and COX-2 inhibitors. This was based on aceclofenac's structural similarity to diclofenac and its metabolism to diclofenac.

Reminder of advice for all NSAIDs
Base the decision to prescribe an NSAID on an assessment of each patient's individual risk factors including any history of cardiovascular and gastrointestinal illness.
Use the lowest effective dose for the shortest duration necessary to control symptoms.
Periodically re-evaluate the patient's need for symptomatic relief and response to treatment.

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6 Yellow Card extended to include devices, counterfeits and defective medicines

We have simplified our medicine and device incident report systems by bringing them all under the Yellow Card Scheme.

You can now report any of the following on a Yellow Card:

- suspected adverse drug reactions
- medical device incidents
- defective medicines
- suspected fake medicines

Please continue to report all suspected adverse drug reactions that are:

- serious, medically significant, or result in harm - serious reactions are any of the following:
  - fatal
  - life-threatening
  - a congenital abnormality
  - disabling or incapacitating
  - those that result in or prolong hospitalisation
- associated with new drugs and vaccines (denoted by a ▼); see list of black triangle medicines

Report via Yellow Card at www.gov.uk/yellowcard.

We have simplified our medicine and device incident report systems by bringing them all under the Yellow Card Scheme. Please report any of the following on a Yellow Card:

- suspected adverse drug reactions (including those caused by medication errors) to medicines, vaccines, and herbal or homeopathic remedies
- medical device incidents
- defective medicines (ie not of an acceptable quality or not working as it should)
- suspected fake medicines

Further information
Further guidance on what to report.
MHRA press release

We will review and seek feedback on these changes from people who use the website and update the website accordingly.

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