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 report that combination use of medicines from different classes of renin-angiotensin system blocking agents is associated with an increased risk of hyperkalaemia, hypotension, and impaired renal function. New warnings have been agreed following an EU-wide review. In particular, prescribers are advised that patients with diabetic nephropathy should not be given an ACE-inhibitor with an angiotensin-receptor blocker as they are already prone to developing hyperkalaemia—see article A1.

Serious hypersensitivity reactions have occurred following ferumoxytol (Rienso) administration in clinical practice worldwide. The European Medicines Agency is currently reviewing the benefits and risks of ferumoxytol. We remind you of the current measures to take to manage and minimise the risk of hypersensitivity reactions with any intravenous iron product—see article A2.

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Drug safety advice

A1 Combination use of medicines from different classes of renin-angiotensin system blocking agents: risk of hyperkalaemia, hypotension, and impaired renal function—new warnings

Combination use of medicines from different classes of renin-angiotensin system blocking agents is associated with an increased risk of hyperkalaemia, hypotension, and impaired renal function. New warnings have been agreed following an EU-wide review. In particular, prescribers are advised that people with diabetic nephropathy should not be given an ACE-inhibitor with an angiotensin-receptor blocker as they are already prone to developing hyperkalaemia. Combining aliskiren with an ACE-inhibitor or angiotensin-receptor blocker is contraindicated in people with kidney impairment or diabetes

The renin-angiotensin hormone system (RAS) controls blood pressure and the volume of fluids in the body. Medicines that have an inhibitory action on the RAS (RAS blocking agents) are used to treat high blood pressure and congestive heart failure. Some are also used to reduce protein loss through the urine in certain kidney disorders. RAS blocking agents fall into three classes: angiotensin-receptor blockers (ARBs, sometimes known as sartans), angiotensin-converting enzyme inhibitors (ACE-inhibitors), and direct renin inhibitors (aliskiren is the only direct renin inhibitor currently marketed in the UK).

Combination use review

An EU review recently concluded that combination use of medicines from two classes of RAS blocking agents is not recommended. The review identified evidence from large clinical trials such as ONTARGET,[1] ALTITUDE,[2] and VA NEPHRON-D[3] and from meta-analyses such as Makani 2013.[4] These studies showed that combination use was associated with an increased risk of hyperkalaemia, hypotension, and impaired renal function compared with using either class of RAS blocking agent alone. No significant benefits of combination use were seen in patients who did not have heart failure.

1. Yusuf S, et al. *N Engl J Med* 2008; **358:** 1547-59.
2. Parving HH, et al. *N Engl J Med* 2012; **367:** 2204-13.
3. Fried LF, et al. *N Engl J Med* 2013; **369:** 1892-1903.
4. Makani H, et al. *BMJ* 2013; **346:** f360.

Heart failure

There is some evidence that the benefits of combination use may outweigh the risks in a selected group of people with heart failure for whom other treatments are unsuitable.[5] Candesartan and valsartan, both ARBs, are the only two RAS blocking agents licensed as add-on therapy to ACE-inhibitors for people with symptomatic heart failure who require such a combination despite optimal therapy.

5. McMurray JJ, et al. *Eur Heart J* 2012; **33:**1787-847.

The triple combination of an ACE-inhibitor, ARB, and a mineralocorticoid receptor antagonist or other potassium-sparing diuretic is not recommended.

Diabetic nephropathy

Prescribers are advised that patients with diabetic nephropathy should not be given an ARB with an ACE-inhibitor as they are already prone to developing hyperkalaemia.

Contraindications

As previously reported, combining aliskiren and an ACE-inhibitor or ARB is strictly contraindicated in people with kidney impairment (estimated glomerular filtration rate [eGFR] <60 mL/minute/1.73 m^2) or diabetes (see the Drug Safety Update article from March 2012).

Drug Safety Update article, March 2012
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON146526

Advice for healthcare professionals:

- Combination use of medicines from two classes of RAS blocking agents (ACE-inhibitors, ARBs, or aliskiren) is not recommended.
- In particular, prescribers are advised not to give patients with diabetic nephropathy an ACE-inhibitor with an ARB since they are particularly prone to developing hyperkalaemia.

- The combination of aliskiren with an ACE-inhibitor or ARB is contraindicated in patients with kidney impairment or diabetes.

Patients with heart failure

- Some patients with heart failure may have a medical need for treatment with an ACE-inhibitor and an ARB. Candesartan and valsartan are licensed as add-on therapy to ACE-inhibitors for people with symptomatic heart failure who require such a combination despite optimal therapy.
- The triple combination of an ACE-inhibitor, ARB, and a mineralocorticoid receptor antagonist or other potassium-sparing diuretic is not recommended.

Patients currently taking a combination of RAS blocking agents

- Review the treatment of all patients currently taking a combination of RAS blocking agents at a routine appointment. Carefully consider if combination use is appropriate.
- If combination use is considered absolutely necessary, it must be carried out under specialist supervision and with close monitoring of blood pressure, renal function, and electrolyte levels (particularly potassium). Consider monitoring patients when combination use is started and on a monthly basis thereafter, and also after changing dose and during intercurrent illness.

Article citation: Drug Safety Update volume 7 issue 11, June 2014: A1.

A2 Ferumoxytol: serious hypersensitivity reactions—reminder of precautions to take before and during administration

New data on serious hypersensitivity reactions following ferumoxytol administration is currently under review by the European Medicines Agency. We remind you of the current measures to take to manage and minimise the risk of hypersensitivity reactions with any intravenous iron product

Previous EU review of intravenous iron

Hypersensitivity reactions are known to occur rarely with all intravenous (IV) iron products and may be life-threatening. Recommendations to manage and minimise this risk were strengthened in 2013 following an EU review. This was reported in Drug Safety Update in August 2013.

Drug Safety Update article, August 2013
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON300398

Risk of hypersensitivity reactions with ferumoxytol

Ferumoxytol was approved in the EU in June 2012 for the IV treatment of iron deficiency anaemia in adults with chronic kidney disease. The recommendations to support safe use from a previous EU-wide review also apply to ferumoxytol and are included in the product information.

Serious hypersensitivity reactions have been reported following use of ferumoxytol in clinical practice. These include anaphylactic reactions, some of which have been fatal. Most of these reports are from the USA where ferumoxytol has been available since 2009. Usage of ferumoxytol in the UK is currently low compared with other IV iron products. There has been one Yellow Card report of a non-fatal hypersensitivity reaction associated with ferumoxytol in the UK.

The benefits and risks of ferumoxytol are currently being closely re-evaluated. The cumulative global reports of hypersensitivity reactions will be taken into consideration. We will communicate any further advice as soon as it is available.

In the meantime we remind you of the current strengthened recommendations for all IV iron products to manage and minimise the risk of serious hypersensitivity reactions:

Advice for healthcare professionals:

Prescribing

- Ferumoxytol products are contraindicated in patients with known hypersensitivity to the active substance or any of the excipients.
- Ferumoxytol is contraindicated in patients with known serious hypersensitivity to other parenteral iron products.
- The risk of hypersensitivity is increased in patients with: known allergies (including drug allergies); immune or inflammatory conditions (eg, systemic lupus erythematosus, rheumatoid arthritis); or those with a history of severe asthma, eczema, or other atopic allergy. In these patients, ferumoxytol should only be used if the benefits are clearly judged to outweigh the risks.

Administration

- Only give ferumoxytol when resuscitation facilities and staff trained to evaluate and manage anaphylactic reactions are immediately available.
- Closely monitor patients for signs of hypersensitivity, including severe hypotension, during and for at least 30 minutes after each administration of ferumoxytol.

Information for patients

- Inform patients of the risk and potential seriousness of a hypersensitivity reaction before every administration of ferumoxytol.
- Inform patients of the relevant symptoms and advise them to tell their doctor or nurse straight away if any of these occur.

Reporting of suspected adverse drug reactions

- Suspected adverse reactions to any IV iron product, including ferumoxytol, should be reported to us on a Yellow Card. Please include the name of the specific product administered (www.mhra.gov.uk/yellowcard).

Further information

Letter sent to healthcare professionals in May 2014
http://www.mhra.gov.uk/home/groups/comms-ic/documents/drugsafetymessage/con425091.pdf

Article citation: Drug Safety Update volume 7 issue 11, June 2014: A2.

Stop press

S1 Ivabradine: emerging clinical trial evidence of increased cardiovascular risk—carefully monitor for bradycardia

Ivabradine (Procorolan) is used to treat symptoms of long-term stable angina in adults with coronary heart disease who have a normal heart rhythm. Ivabradine is also used in patients with long-term heart failure who have a normal heart rhythm but whose heart rate is at least 75 beats per minute (bpm).

The SIGNIFY trial investigated the efficacy of ivabradine compared with placebo in people with coronary artery disease. The ivabradine dose regimen used in the trial (7.5 to 10 mg twice daily) was higher than the licensed posology (5 to 7.5 mg twice daily). The trial included a pre-specified subgroup analysis of participants with symptomatic angina of CCS class II or more. Preliminary results have shown a small but statistically significant increase in the combined risk of cardiovascular death and non-fatal myocardial infarction with ivabradine compared with placebo in this subgroup. This cardiovascular risk might be associated with a target heart rate below 60 bpm.

The European Medicines Agency is reviewing how the data from the SIGNIFY study impact the balance of benefits and risks of ivabradine. While the review is ongoing, we remind you of the following:

Advice for healthcare professionals:

Posology and monitoring

- The starting dose of ivabradine is 5 mg twice daily. The maintenance dose should not exceed 7.5 mg twice daily.
- Carefully monitor patients for bradycardia or its symptoms (eg, dizziness, fatigue, hypotension).
- Down-titrate the dose if resting heart rate decreases persistently below 50 bpm or if the patient experiences symptoms of bradycardia. The dose can be down-titrated to 2.5 mg twice daily if necessary.
- Stop ivabradine treatment if the resting heart rate remains below 50 bpm or symptoms of bradycardia persist.
- Only increase the dose to 7.5 mg twice daily after 3 to 4 weeks of treatment and if the 5 mg dose is well tolerated but insufficient. Carefully monitor the effect of a dose increase on heart rate.

Other considerations

- Avoid concomitant use of ivabradine with heart rate-reducing calcium channel blockers such as verapamil or diltiazem.
- Review the treatment of patients currently using ivabradine where appropriate.

Further information
European Medicines Agency statement 8 May 2014
http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/05/WC500166318.pdf

Letter sent to healthcare professionals in June 2014
http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con428306.pdf

Article citation: Drug Safety Update volume 7 issue 11, June 2014: S1.

S2 **Chlorhexidine solutions: risk of chemical burn injury to skin in premature infants**

Bloodstream infections are an important cause of morbidity and mortality in neonatal intensive care units. Before and during neonatal catheterisation, skin disinfection and aseptic technique are crucial for preventing catheter-related bloodstream infections. Chlorhexidine is an antiseptic frequently used for skin disinfection before catheterisation of premature infants.

We have received 13 reports of serious side effects in premature infants who were treated with chlorhexidine solution before central venous catheterisation (umbilical catheterisation or long line insertion). Another 16 cases were identified in the medical literature. The side effects included erythema and chemical burns with and without skin loss. Four of these cases had a fatal outcome, although severe complications of prematurity might have contributed to two of the fatal cases. The chemical injuries occurred in infants of less than 32 weeks gestation and within the first few days of life when alcohol based chlorhexidine solutions (0.5% or 2% in 70% alcohol) or 2% aqueous chlorhexidine solutions were used.

This issue will be reviewed at a European level. We will publish the outcomes of the review and any regulatory changes.

Advice for healthcare professionals:

- When using alcohol-based or water-based chlorhexidine solutions on preterm infants, bear in mind the risk of severe chemical injuries.
- Use the minimum amount of chlorhexidine solution required and do not allow the solution to pool. Remove any excess solution and any soaked materials, drapes, or gowns from the skin.
- Monitor patients frequently to detect and manage cutaneous side effects at an early stage.
- Please report any similar events through the Yellow Card Scheme: www.mhra.gov.uk/yellowcard. Your reports will contribute to the European review.

Further information

Lashkari et al. *Arch Dis Child Fetal Neonatal Ed* 2012; **97:** F64
http://fn.bmj.com/content/97/1/F64.full.html

Article citation: Drug Safety Update volume 7 issue 11, June 2014: S2.

Yellow Card Scheme update

Y1 **E-learning modules on adverse drug reactions**

With around 1 in 15 hospital admissions attributed to adverse drug reactions, a series of e-learning modules on adverse drug reactions was launched this month. NHS Education for Scotland and the Yellow Card Centre of Scotland have jointly published the six modules, which introduce the healthcare professional to basic characteristics of adverse reactions and lay down the principles of recognising and avoiding them. The final module covers pharmacovigilance.

These e-learning modules are written for doctors, nurses and pharmacists—they are especially suited for those in foundation training programmes and those requiring an update in this area for their continuing professional development. The modules will ensure that all healthcare professionals attain a consistent standard of understanding on adverse drug reactions. Learners will also become more confident about when and how to report adverse drug reactions on Yellow Cards.

The adverse drug reaction e-learning modules can be found at:
http://www.nes.scot.nhs.uk/education-and-training/by-discipline/pharmacy/about-nes-pharmacy/educational-resources/resources-by-topic/clinical-governance/patient-safety-adverse-drug-reactions.aspx

Article citation: Drug Safety Update volume 7 issue 11, June 2014: Y1.