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 that there was no significant difference in mortality between tiotropium delivered via Respimat compared with Handihaler in the TIOSPIR trial. Take the risk of cardiovascular side effects into account when prescribing tiotropium delivered via Respimat or Handihaler to patients with certain cardiac conditions, who were excluded from clinical trials of tiotropium (including TIOSPIR)—see article 1.

A valve defect might stop gas delivery early in some INOmax (nitric oxide) cylinders. While this defect is still being investigated, we remind you to always have a full spare cylinder loaded on the delivery device so the cylinders can be switched without delay—see article 2.

We remind you that a new offence of driving with certain medicines above specified limits in the blood will be enforced from 2nd March 2015 in England and Wales. Talk to patients who are on medicines with potential to impair driving and discuss the patient leaflet advice—see article 3.

In each issue of Drug Safety Update we will now summarise drug safety letters sent to healthcare professionals that are not linked to their own Drug Safety Update article. Since November 2014, letters were sent regarding vismodegib (Erivedge▼), chlorhexidine solutions, carbocisteine oral liquid (Mucodyne Paediatric 125mg/5ml), regadenoson (Rapiscan), a parenteral nutrition emulsion (Triomel), and telavancin (Vibativ▼)—see article 4.

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1 **Tiotropium delivered via Respimat compared with Handihaler: no significant difference in mortality in TIOSPIR trial**

Take the risk of cardiovascular side effects into account when prescribing tiotropium delivered via Respimat or Handihaler to patients with certain cardiac conditions, who were excluded from clinical trials of tiotropium (including TIOSPIR).

When using tiotropium delivered via Respimat or Handihaler to treat chronic obstructive pulmonary disease (COPD):

- take the risk of cardiovascular side effects into account for patients with conditions that may be affected by the anticholinergic action of tiotropium, including:
  - myocardial infarction in the last 6 months
  - unstable or life threatening cardiac arrhythmia
  - cardiac arrhythmia requiring intervention or a change in drug therapy in the past year
  - hospitalisation for heart failure (NYHA Class III or IV) within the past year
- tell these patients to report any worsening of cardiac symptoms after starting tiotropium; patients with these conditions were excluded from clinical trials of tiotropium, including TIOSPIR
- review the treatment of all patients already taking tiotropium as part of the comprehensive management plan to ensure that it remains appropriate for them; regularly review treatment of patients at high risk of cardiovascular events
- remind patients not to exceed the recommended once daily dose
- continue to report suspected side effects to tiotropium or any other medicine on a Yellow Card: www.gov.uk/yellowcard

Tiotropium (Spiriva) is licensed as a maintenance bronchodilator treatment to relieve symptoms of COPD. Tiotropium can be delivered in two ways:

1. via the HandiHaler inhaler once daily, from a capsule containing 18 micrograms of tiotropium
2. via the soft-mist Respimat inhaler taken as two puffs once daily (2.5 micrograms of tiotropium delivered per puff)

TIOSPIR clinical trial

Previous studies of tiotropium suggested that more people died while using tiotropium Respimat compared with placebo and with tiotropium HandiHaler. Previous advice was to use tiotropium Respimat with caution in patients with known cardiac rhythm disorders.[1]

The TIOSPIR clinical trial[2] compared the safety and efficacy of tiotropium delivered via Respimat (2.5 micrograms or 5 micrograms once daily) with tiotropium delivered via HandiHaler (18 micrograms once daily). TIOSPIR included 17,135 participants with COPD who were followed up for a mean of 2.3 years. The primary safety outcome was the time to death from any cause, which was used to calculate the relative risk of death between groups. The primary efficacy outcome was time to first exacerbation of COPD. Cardiovascular safety was also assessed.

Results

There was no significant difference in the risk of death from any cause between tiotropium Respimat 5 micrograms or 2.5 micrograms compared with tiotropium HandiHaler (tiotropium Respimat 5 micrograms vs tiotropium HandiHaler 18 micrograms*: hazard ratio, 0. 96; 95% confidence interval [CI], 0.84 to 1.09). The incidences of different causes of death (including death due to cardiovascular events) and incidences of major cardiovascular adverse events were similar across the three groups. There was no significant difference in the risk of the first exacerbation of COPD (tiotropium Respimat 5 micrograms vs tiotropium HandiHaler 18 micrograms: hazard ratio, 0.98; 95% CI, 0.93 to 1.03).

1. 'Tiotropium: safety studies of Spiriva Respimat' Drug Safety Update Nov 2011 volume 4, issue 4: H2 (viewed February 2015)

2. Wise R and others. 'Tiotropium Respimat Inhaler and the Risk of Death in COPD' New England Journal of Medicine 2013: volume 369, pages1491-1501. (viewed February 2015)

*Data are not shown for tiotropium Respimat 2.5 micrograms because tiotropium Respimat 5 micrograms is the licensed dose. See publication referenced above[2] for tiotropium Respimat 2.5 micrograms data.

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In participants with previous cardiac arrhythmia there was no significant difference in the risk of death from any cause between tiotropium Respimat 5 micrograms and tiotropium HandiHaler 18 micrograms (hazard ratio, 0.81; 95% CI, 0.58 to 1.12).

Further information
Tiotropium Respimat summary of product characteristics

Tiotropium HandiHaler summary of product characteristics

Implications for clinical practice
In light of the results of TIOSPIR and other clinical trials, we have added the warning to use tiotropium with caution in the patients listed above to the tiotropium summaries of product characteristics.

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2 **INOmax (nitric oxide) cylinders: valve defect might stop gas delivery early in some cylinders**

While this defect is still being investigated, we remind you to always have a full spare cylinder loaded on the delivery device so the cylinders can be switched without delay.

When using nitric oxide cylinders, we remind you:

- to always have a full spare cylinder loaded on the delivery device so the cylinders can be switched without delay
- to always deliver INOmax using devices with pressure sensor monitors and gas monitor alarms - the low pressure alarm will sound if the valve closes
- that devices without low pressure alarms are not safe to use
- to purge the regulator of the second cylinder when switching cylinders, before connecting it to the delivery device - this prevents excess NO_2 formation
- to take extra care during patient transfer - always have back-up cylinders available, even for a short transfer
- report any suspected defective cylinder valves on a Yellow Card: www.gov.uk/yellowcard

A defect has been reported and this might cause the valves in some INOmax (nitric oxide) cylinders to close while in use, before the cylinder is empty. This abruptly stops gas delivery earlier than expected. Unless the cylinder is changed immediately, the following life-threatening rebound effects can occur:

- increase in pulmonary artery pressure
- decrease in oxygen saturation
- cardiovascular collapse

This applies to 400 ppm and 800 ppm cylinders of 2 L and 10 L capacity. It is not possible to identify defective cylinder valves in the hospital setting.

The licence-holder is investigating an incident that might be linked to this valve defect (the patient did not experience any adverse events related to this incident) and the cause of the defect.

Switching to alternative products
Nitric oxide products other than INOmax are available but may have different concentrations of nitric oxide and different cylinder fill pressures. Also, it may be necessary to change the hardware or software of the nitric oxide delivery system when switching between products. If you switch from INOmax to another nitric oxide product, ensure that:

- the delivery system is compatible with the new nitric oxide product
- staff are trained with the new product and familiar with any new connections and dosing schedules

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Licensed indication
INOmax, in conjunction with ventilatory support and other appropriate active substances, is indicated:

- for the treatment of newborn infants ≥34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation
- as part of the treatment of peri- and post-operative pulmonary hypertension in adults and newborn infants, infants and toddlers, children and adolescents, ages 0-17 years in conjunction to heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation

Further information
Letter sent to healthcare professionals in December 2014

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3 **Drugs and driving: blood concentration limits set for certain drugs**
In July 2014 we informed you of a new offence of driving with certain medicines above specified limits in the blood. This new offence will be enforced from 2nd March 2015 in England and Wales.* The new offence does not replace any existing offences of driving whilst impaired by drugs, including licensed medicines.

*The date of enforcement in Scotland is dependent on approval of regulations by the Scottish Parliament. The introduction of a similar offence in Northern Ireland is under consideration.

Advice for healthcare professionals:
Any condition requiring medical treatment may itself pose a risk to driving ability if left untreated. Therefore it is important for patients to continue their treatment.

Advice to give to patients:

- it is against the law to drive if your driving ability is impaired by any medicine
- if you are taking your medicine as directed and your driving is not impaired, then you are not breaking the law
- check the leaflet that comes with your medicine for information on how your medicine may affect your driving ability
- do not drive while taking this medicine until you know how it affects you
- do not drive if you feel sleepy, dizzy, unable to concentrate or make decisions, or if you have blurred or double vision

Further information
Information leaflet to give to patients

Information for the public from the Department for Transport

Additional guidance for healthcare professionals from the Department for Transport

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4 **Letters sent to healthcare professionals since November 2014**
In each issue of Drug Safety Update we will now summarise drug safety letters sent to healthcare professionals that are not linked to their own Drug Safety Update article. Since November 2014, letters were sent regarding:

- Telavancin (Vibativ▼): recommendations for use and important risks (nephrotoxicity, QTc prolongation, reproductive toxicity and off-label use) – sent by Clinigen on 12 November 2014
- Parenteral nutrition emulsion (Triomel): medication errors - reminder of the importance of correct preparation and administration – sent by Baxter on 14 November 2014
- Regadenoson (Rapiscan): New important advice to minimise the risk of cerebrovascular accident and prolongation of Rapiscan-induced seizures following administration of aminophylline – sent by Rapidscan Pharma Solutions on 19 December 2014
- Carbocisteine oral liquid (Mucodyne Paediatric 125mg/5ml) will not be available after April 2015 – sent by Sanofi on 22 January 2015
- Chlorhexidine solutions: risk of chemical burn injury to skin in premature infants – sent by the MHRA on 29 January 2015
- Vismodegib (Erivedge ▼): important changes to the management of the UK pregnancy prevention programme to minimise the risk of teratogenicity – sent by Roche in January 2015.

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