Drug Safety Update

MHRA

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**

Volume 8, Issue 4, **November 2014**

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 remind you that the antidepressant agomelatine (Valdoxan) may cause liver toxicity in some people. Test liver function before and during treatment. Do not start or continue treatment if serum transaminases exceed three times the upper limit of normal. Advise patients to stop taking agomelatine and to get medical help immediately if they have any signs or symptoms of liver injury—see article A1.

We have received reports of Colobreathe (colistimethate sodium) capsules shattering when pierced by their inhaler device. Colobreathe is indicated for the management of chronic *P. aeruginosa* lung infections in patients with cystic fibrosis. The instructions for inhaler use have been revised to reduce this risk. Demonstrate the new inhaler instructions to patients and carers, supervise the first dose, and tell patients and carers to refer to the instructions in the patient information leaflet—see article A2.

Boceprevir (Victrelis) and telaprevir (Incivo) for treatment of hepatitis C are not recommended for patients who have a low platelet count or hypoalbuminaemia before starting either of these medicines. Boceprevir is also not recommended for patients who have coagulopathy before starting it—see article S1.

In December 2013 we told you of the risk of serious vascular occlusive events with the antileukaemic agent ponatinib (Iclusig▼) and highlighted preliminary advice on risk minimisation. An in-depth EU review of this risk has now been completed—see article S2.

We remind you that there is a risk of severe chemical injuries associated with the use of both alcohol-based and water-based chlorhexidine solutions for skin disinfection in premature infants. Use the minimum amount of chlorhexidine solution required and do not allow the solution to pool on or under the infant. Remove any excess solution and any soaked materials, drapes, or gowns from the skin—see article S3.

Finally, don't miss the latest drug safety advice! We are changing our arrangements for sending out email alerts about Drug Safety Update. To get the very latest drug safety news and drug alerts as soon as they are released, check that you're signed up here: https://service.govdelivery.com/accounts/UKMHRA/subscriber/new?topic_id=UKMHRA_0044

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Drug safety advice

A1 Agomelatine (Valdoxan): risk of liver toxicity—reminder to test liver function before and during treatment

Agomelatine (Valdoxan) may cause liver toxicity in some people. Test liver function before and during treatment. Do not start or continue treatment if serum transaminases exceed three times the upper limit of normal. Advise patients to stop taking agomelatine and to get medical help immediately if they have any signs or symptoms of liver injury

Agomelatine (Valdoxan) is a melatonergic antidepressant used to treat major depressive disorder in adults.

Drug Safety Update article from October 2012: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON199558

Liver toxicity is a side effect of agomelatine (see Drug Safety Update article from October 2012).

A recent European review revealed poor clinical compliance with recommended liver function monitoring. We therefore remind you to test liver function before starting agomelatine and regularly during treatment (see below).

We are working with the licence-holder to produce a booklet for prescribers to give to patients when prescribing agomelatine. This will inform patients of the risk of liver injury, the symptoms and signs to look out for, and the importance of regular blood tests.

Not recommended for patients over 75
We also remind you that the efficacy of agomelatine has not been established in patients over 75 years. Agomelatine is not recommended in this age-group.

Advice for healthcare professionals:

- Perform baseline liver function tests in every patient before starting treatment with agomelatine.
- Do not start treatment if serum transaminases exceed three times the upper limit of normal.
- Monitor liver function at 3, 6, 12, and 24 weeks after starting treatment and regularly thereafter when clinically indicated.
- Stop treatment immediately if serum transaminases exceed three times the upper limit of normal, or if patients have symptoms or signs of suspected liver injury.
- Tell patients to watch out for the symptoms and signs of liver injury (eg, jaundice, dark urine, bruising). Explain the importance of regular liver function monitoring.
- Advise patients to stop taking agomelatine and to get medical help immediately if they have any signs or symptoms of liver injury.

Please report any suspected cases of liver toxicity or other side effects via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard)

Further information
European Medicines Agency press release, September 2014: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/09/news_detail_002173.jsp&mid=WC0b01ac058004d5c1

Article citation: Drug Safety Update volume 8 issue 4, November 2014: A1

A2 Colobreathe (colistimethate sodium dry powder for inhalation): risk of capsule breakage—new instructions for use

We have received reports of Colobreathe (colistimethate sodium) capsules shattering when pierced by their inhaler device. The instructions for inhaler use have been revised to reduce this risk. Demonstrate the new inhaler instructions to patients and carers and supervise the first dose (see below)

Colobreathe (colistimethate sodium dry powder for inhalation) is indicated for the management of chronic *Pseudomonas aeruginosa* lung infections in patients with cystic fibrosis aged 6 years and older. We remind you to consider official guidance on the appropriate use of antibiotics when prescribing Colobreathe.

Colistimethate sodium is inhaled as a powder from a gelatine capsule using the supplied inhaler device. A piston within the inhaler pierces the capsule allowing the capsule contents to be inhaled.

To date, we have received 26 Yellow Card reports* of capsules shattering when pierced. The filter in the inhaler catches pieces of broken capsule shell more than 2 mm wide. However, smaller pieces could be swallowed or inhaled. Some reports of broken capsules have been associated with throat irritation and coughing, although there are no serious safety concerns and patients need not be alarmed if this happens.

The manufacturer has revised the instructions for inhaler use to reduce the risk of capsules breaking. These revised instructions have been included in the patient information leaflet and summary of product characteristics (see left).

*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

Advice for healthcare professionals:

- Demonstrate the new inhaler instructions to patients. The key points are:
  - insert the capsule widest end first into the inhaler chamber.
  - pierce the capsule gradually using a two-step process
  - only pierce each capsule once
- Supervise patients taking their first dose.
- Tell patients and carers to refer to the instructions in the patient information leaflet that comes in the pack.

Further information
Colobreathe summary of product characteristics:
http://www.medicines.org.uk/emc/medicine/27647

Colobreathe patient information leaflet (with updated instructions for use)
http://www.medicines.org.uk/emc/PIL.27801.latest.pdf

Article citation: Drug Safety Update volume 8 issue 4, November 2014: A2

Stop press

S1 Boceprevir (Victrelis) and telaprevir (Incivo): baseline predictive factors for sepsis, worsening liver function, and mortality

Boceprevir (Victrelis) and telaprevir (Incivo) are protease inhibitors indicated for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease.

A European review identified the following baseline markers as predictive factors for morbidity requiring hospitalisation (eg, sepsis, worsening liver function) and mortality in cirrhotic patients treated with either boceprevir or telaprevir in combination with peginterferon alfa and ribavirin:

- low platelet count
- hypoalbuminaemia
- coagulopathy (for boceprevir only)

Boceprevir and telaprevir are not recommended for patients who have a low platelet count or hypoalbuminaemia before starting either of these medicines. Boceprevir is also not recommended for patients who have coagulopathy before starting it. If treatment is started, closely monitor for infection, worsening liver function, and anaemia, as described in the summary of product characteristics (see left).

Further information
Boceprevir summary of product characteristics
https://www.medicines.org.uk/emc/medicine/24768

Telaprevir summary of product characteristics
https://www.medicines.org.uk/emc/medicine/25038

Article citation: Drug Safety Update volume 8 issue 4, November 2014: S1

S2 **Ponatinib (Iclusig▼): risk of vascular occlusive events**

Ponatinib summary of product characteristics
https://www.medicines.org.uk/emc/medicine/28145

Drug Safety Update, December 2013
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON350695

Full recommendations:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Iclusig/human_referral_prac_000033.jsp&mid=WC0b01ac05805c516f

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, please see the summary of product characteristics.

In December 2013 we told you of the risk of serious vascular occlusive events with ponatinib (Iclusig▼) and highlighted preliminary advice on risk minimisation. An in-depth EU review of this risk has now been completed. The full recommendations have been published by the European Medicines Agency.

To summarise, the available evidence shows that the risk of blood vessel blockage with ponatinib is likely to be dose-dependent. However, the data are insufficient to recommend reducing the ponatinib dose. Also, there is a risk that a lower dose might not be as effective as the current dose in all patients and in long-term treatment. Therefore, the recommended starting dose of ponatinib remains at 45 mg once a day.

The product information will be updated with strengthened warnings about the risks associated with ponatinib. The latest evidence will also be added in case you wish to consider reducing the dose in patients with chronic phase chronic myeloid leukaemia who are responding well to treatment, and who might be at high risk of blood vessel blockage. Stop ponatinib if a complete response has not occurred within 3 months of treatment and monitor patients for high blood pressure or signs of heart problems.

Call for reporting
Please continue to report any suspected adverse reactions to ponatinib or any other medicine via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard)

Article citation: Drug Safety Update volume 8 issue 4, November 2014: S2

S3 **Chlorhexidine solutions: reminder of the risk of chemical burns in premature infants**

Drug Safety Update, June 2014
http://webarchive.nationalarchives.gov.uk/+/http://www.mhra.gov.uk/safetyinformation/drugsafetyupdate/con428307

In June 2014 we informed you of the risk of severe chemical injuries associated with the use of both alcohol-based and water-based chlorhexidine solutions for skin disinfection in premature infants. This was based on Yellow Card reports and reports identified in the literature. A European review has since considered the MHRA evidence together with additional information from spontaneous reporting and published literature. This European review confirmed our findings. The risk appears to be higher in infants born before 32 weeks of gestation than in full term infants and in the first 2 weeks of life than in later life.

The advice for healthcare professionals remains the same as that published in June 2014:

Advice for healthcare professionals:

- When using alcohol-based or water-based chlorhexidine solutions on premature 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 adverse events through the Yellow Card Scheme: www.mhra.gov.uk/yellowcard

Further information
European review
http://www.ema.europa.eu/docs/en_GB/document_library/PRAC_recommendation_on_signal/2014/09/WC500174026.pdf

Single-use containers preferred
Chlorhexidine solutions are available in single-use containers or multiple-use ones. Use single-use containers where possible. There is a danger of accidentally using too much solution from a multiple-use container.

Article citation: Drug Safety Update volume 8 issue 4, November 2014: S3

S4 **Desiccants in blister packs: reminder of risk of ingestion**

Take care to tell people receiving blister packs containing a desiccant that the desiccant should not be swallowed.

During the past two months, we have received two reports of people swallowing the desiccant that came with their Nicorandil tablets instead of the tablet itself. Neither person suffered any adverse effects.

The foil of blister packs containing desiccant is clearly labelled to show which blister pocket contains the desiccant. The accompanying patient information leaflet also advises people not to swallow the desiccant.

Article citation: Drug Safety Update volume 8 issue 4, November 2014: S4

Other information from the MHRA

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Article citation: Drug Safety Update volume 8 issue 4, November 2014: O1