

# 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

Volume 11 Issue 1 August 2017

### Contents

<b>Ibrutinib (Imbruvica ▼): reports of ventricular tachyarrhythmia; risk of hepatitis B reactivation and of opportunistic infections</b>	page 2
<b>Corticosteroids: risk of central serous chorioretinopathy with local as well as systemic administration</b>	page 4
<b>Adrenaline auto-injectors: updated advice after European review</b>	page 5
<b>Letters sent to healthcare professionals in July 2017</b>	page 7
<b>Medical Device Alerts issued in July 2017</b>	page 7

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency 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.



MHRA is accredited by NICE to provide Drug Safety Update. Further information can be found on the NICE Evidence Search portal: [www.evidence.nhs.uk/](http://www.evidence.nhs.uk/)

This month, we feature advice about ibrutinib (Imbruvica ▼), indicated for certain haematological malignancies. Cases of ventricular tachyarrhythmia have been reported during ibrutinib treatment. Temporarily discontinue ibrutinib in patients who develop symptoms suggestive of ventricular arrhythmia and assess benefit-risk before restarting therapy. We also give updated guidance aiming to minimise risk of hepatitis B virus reactivation and opportunistic infections. Establish hepatitis B virus status before initiating treatment with ibrutinib. In patients with positive hepatitis B serology, consultation with a liver disease expert is recommended before starting treatment. Consider prophylaxis for patients who are at an increased risk of opportunistic infections.

In the second article (page 4), read about reports of central serous chorioretinopathy during the administration of corticosteroids. This rare adverse event has been reported not only after use of systemic corticosteroids but also after local administration of topical corticosteroids. Tell patients to report any vision problems during treatment with corticosteroids. If any patients present with vision problems, consider referral to an ophthalmologist.

In the final article, we have an update on advice for adrenaline auto-injectors (page 5). It is recommended that 2 adrenaline auto-injectors are prescribed, which patients should carry at all times. It is also important that patients and caregivers are trained how to use the particular device prescribed. Use the links to educational materials when reviewing the instructions and operation of prescribed adrenaline auto-injectors with patients and caregivers.

[drugsafetyupdate@mhra.gov.uk](mailto:drugsafetyupdate@mhra.gov.uk)

## **Ibrutinib (Imbruvica ▼): reports of ventricular tachyarrhythmia; risk of hepatitis B reactivation and of opportunistic infections**

Temporarily discontinue ibrutinib in patients who develop symptoms suggestive of ventricular arrhythmia and assess benefit-risk before restarting therapy. Establish hepatitis B virus status before initiating ibrutinib. Consider prophylaxis for patients who are at an increased risk of opportunistic infections.

### **Advice for healthcare professionals:**

- cases of ventricular tachyarrhythmia have been reported
- temporarily discontinue ibrutinib in patients who develop symptoms suggestive of ventricular arrhythmia, including palpitations, chest pain, dyspnoea, dizziness, or fainting, and assess benefit-risk before restarting therapy
- be aware of the risk of hepatitis B virus reactivation and establish hepatitis B virus status before initiating therapy
- for patients with positive hepatitis B serology, consultation with a liver disease expert is recommended before the start of treatment; monitor and manage patients according to local medical standards of care to minimise the risk of hepatitis B virus reactivation
- consider prophylaxis according to standard of care for patients who are at an increased risk of opportunistic infections

### **Routine European review**

A routine European review examined the safety profile of ibrutinib. Data from randomised controlled trials and the scientific literature were assessed. Worldwide spontaneous suspected adverse drug reaction (ADR) reports were also reviewed from a cumulative post-marketing exposure of approximately 38,000 patient-years.

### **Ventricular tachyarrhythmia**

Randomised controlled trials reported a slightly increased risk of ventricular tachyarrhythmia with ibrutinib. In a 2017 study of case reports of relevant events from post-marketing sources and clinical trial data,<sup>1</sup> the authors identified 11 cases of ventricular tachycardia/ventricular fibrillation and 6 cases of sudden cardiac death in patients exposed to ibrutinib. In 12 of these 17 cases, the events occurred without any evidence of prior cardiac history.

The review also identified 2 spontaneous ADRs of ventricular tachyarrhythmia in which the role of ibrutinib could not be excluded.

The product information of ibrutinib is being updated to include ventricular tachyarrhythmia as a common adverse reaction (thought to occur in fewer than 10 in 100 patients taking ibrutinib post-marketing).

Temporarily discontinue ibrutinib in patients who develop signs or symptoms of ventricular tachyarrhythmia, including, but not limited to, palpitations, chest pain, dyspnoea, dizziness, or fainting. Perform a complete clinical benefit-risk assessment before possibly restarting therapy.

1. Lampson BL, et al. [Ventricular arrhythmias and sudden death in patients taking ibrutinib](#). *Blood* 2017 129: 2581–84.

Ibrutinib (Imbruvica ▼). [Summary of Product Characteristics](#) (SmPC).

## **Hepatitis B virus reactivation**

Data for hepatitis B virus reactivation were not available from clinical trials since all patients had been pre-screened for hepatitis B status and those who tested positive were excluded from studies.

The review identified 8 cases of hepatitis B reactivation in which the role of ibrutinib was considered probable or possible.

The product information of ibrutinib is being updated to include hepatitis B virus reactivation as an uncommon adverse reaction (see [letter to healthcare professionals](#)).

Establish hepatitis B virus status before initiating treatment with ibrutinib. In patients with positive hepatitis B serology, consultation with a liver disease expert is recommended before starting treatment.

Patients with positive hepatitis B serology who require ibrutinib should be monitored and managed according to local medical standards of care to minimise the risk of hepatitis B virus reactivation.

## **Opportunistic infections**

Infections are a frequent co-morbidity in patients with the haematological malignancies in which ibrutinib is indicated.

The product information for ibrutinib already lists opportunistic infections as very common adverse reactions (thought to affect more than 10 in 100 patients taking the drug post-marketing).

The review identified 157 cases of aspergillosis among patients exposed to ibrutinib in post-marketing settings, 43 of which were fatal. The review also identified 44 cases of *Pneumocystis Jirovecii* pneumonia (PJP), none of which were fatal. In clinical trials, ibrutinib did not appear to raise the risk of aspergillosis or PJP compared with comparator treatments.

Given the relatively high number of fatal cases, healthcare professionals should consider prophylaxis according to standard of care for all patients who are at an increased risk of opportunistic infections.

## **Background**

Ibrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK), involved in the maturation of B-cells.

Ibrutinib is indicated for the treatment of adult patients with:

- mantle cell lymphoma who have received at least one prior therapy
- chronic lymphocytic leukaemia (CLL), including CLL with deletion 17p
- Waldenström's macroglobulinaemia

## **Call for reporting**

This product is subject to additional monitoring. Report any suspected adverse drug reactions associated with ibrutinib to us on a [Yellow Card](#).

*Article citation: Drug Safety Update volume 11 issue 1, August 2017: 1*

## Corticosteroids: rare risk of central serous chorioretinopathy with local as well as systemic administration

Central serous chorioretinopathy is a retinal disorder that has been linked to the systemic use of corticosteroids. Recently, it has also been reported after local administration of corticosteroids via inhaled and intranasal, epidural, intra-articular, topical dermal, and periocular routes.

### Advice for healthcare professionals:

- advise patients to report any blurred vision or other visual disturbances during corticosteroid treatment
- consider referral to an ophthalmologist for evaluation of possible causes if a patient presents with vision problems
- report suspected adverse reactions to us on a [Yellow Card](#)

### Background

Corticosteroids are indicated for a wide variety of indications in the treatment or suppression of inflammatory and allergic disorders, commonly including:

- asthma and allergic rhinitis
- systemic inflammatory disorders, for example, rheumatoid arthritis
- skin conditions, for example, eczema

### Central serous chorioretinopathy

Central serous chorioretinopathy (CSCR) is characterised by the accumulation of subretinal fluid at the posterior pole of the fundus, ultimately causing retinal detachment. CSCR typically affects one eye only and can cause vision to be blurry and distorted, with objects often appearing smaller and distorted in the affected eye. Patients may also have difficulty with bright lights and contrast sensitivity.

Although the exact mechanism that leads someone to develop CSCR is unknown, several possible risk factors have been described, including use of systemic corticosteroids, pregnancy, and Cushing's syndrome.<sup>1</sup> These risks are thought to be associated with the effect of cortisol on the eye.

CSCR has recently also been described after local administration of corticosteroids via inhaled and intranasal, epidural, intra-articular, topical dermal, and periocular routes.<sup>2,3,4,5,6</sup> It is a rare side effect that occurs with all formulations.

Although blurred vision is a symptom of CSCR, it is also an established side effect of steroid treatment. The causes of blurred vision are various and can also include cataract and glaucoma.

Inform patients they should report any vision problems or disturbances. If a patient who has received local treatment with a corticosteroid presents with visual symptoms, consider referral to an ophthalmologist for evaluation of possible causes.

*Article citation: Drug Safety Update volume 11 issue 1, August 2017: 2.*

1. Royal National Institute of Blind People. [Central Serous Retinopathy](#). Accessed August 2017.

2. Chan LY, et al. [Localized topical steroid use and central serous retinopathy](#). J Dermatolog Treat 2016; 27: 425–26.

3. Ricketti PA, et al. [Central serous chorioretinopathy secondary to corticosteroids in patients with atopic disease](#). Allergy Asthma Proc 2015; 36: 123–29.

4. Kleinberger AJ, et al. [Bilateral central serous chorioretinopathy caused by intranasal corticosteroids: a case report and review of the literature](#). Laryngoscope 2011; 121: 2034–37.

5. Tliba A, et al. [Central serous chorioretinopathy secondary to epidural corticosteroid infiltration. Tunis Med](#) 2016; 94: 166

6. Balakrishnan S, et al. [Sudden loss of visual acuity following intra-articular steroid injection in to the knee joint: a case report](#). Cases J 2008; 1: 428.

## **Adrenaline auto-injectors: updated advice after European review**

It is recommended that 2 adrenaline auto-injectors are prescribed, which patients should carry at all times.

### **Advice for healthcare professionals:**

- it is recommended that 2 adrenaline auto-injectors are prescribed, which patients should carry at all times
- ensure that people with allergies and their carers have been trained to use the particular auto-injector that they have been prescribed—technique varies between injectors
- encourage people with allergies and their carers to obtain and practise using a trainer device (available for free from the manufacturers' websites)

### **Advice to give to people with allergies and their carers:**

- it is recommended that you carry 2 adrenaline auto-injectors at all times; this is particularly important for people who also have allergic asthma because they are at increased risk of a severe anaphylactic reaction
- use the adrenaline auto-injector at the first signs of a severe allergic reaction
- take the following actions immediately after every use of an adrenaline auto-injector:
  1. call 999, ask for an ambulance and state “anaphylaxis”, even if symptoms are improving
  2. lie flat with legs raised to maintain blood flow. However, if you have breathing difficulties, you may need to sit up to make breathing easier
  3. seek help immediately after using the auto-injector and if at all possible make sure someone stays with you while waiting for the ambulance
  4. if you do not start to feel better, use the second auto-injector 5–15 minutes after the first one
- check the expiry date of the adrenaline auto-injectors and obtain replacements before they expire; expired injectors will be less effective

### **Results of European review**

The European Medicines Agency (EMA) has completed a [review of all adrenaline auto-injectors](#) approved in the EU. The review concluded that:

- due to uncertainties about the site of drug delivery and the speed of adrenaline action within the body, it is recommended that healthcare professionals prescribe 2 auto-injectors, which patients should carry at all times
- the needle length of the device is now stated in the product information because this may be an important factor for the prescriber to consider when choosing a suitable auto-injector
- the training of patients and their carers in the correct use of the product is important and manufacturers were required to update their educational materials – see table
- manufacturers should carry out studies in humans to more fully understand when and how much adrenaline reaches the blood stream, and how quickly and effectively it acts on body tissues when given through an auto-injector – these studies have started and will help to inform future recommendations for adrenaline auto-injectors

## Patient and carer instructions

If you prescribe adrenaline auto-injectors, you should ensure that the patient or carer thoroughly understands the indications and use of the device.

You should review with the patient and their carers the instructions and operation of the adrenaline auto-injector.

We have produced an updated [advice sheet to give to patients and carers](#).

The table below provides links to the patient information leaflets and educational material for all adrenaline auto-injectors licenced in the UK. People with allergies and their carers can also use manufacturer websites to order trainer devices and to sign up for expiry alert services.

Product name	Patient information leaflet	Educational material produced by the manufacturer
Emerade 150 µg, 300 µg, and 500 µg solution for injection in pre-filled pen	<a href="#">Emerade adrenaline auto-injectors</a>	Emerade <a href="#">patient brochure</a> and <a href="#">instruction video</a>
EpiPen 0.3 mg and EpiPen Jr. 0.15 mg adrenaline (epinephrine) auto-injector	<a href="#">EpiPen</a> and <a href="#">EpiPen Jr</a> auto-injectors	EpiPen <a href="#">user guide</a> and <a href="#">instruction video</a>
Jext 150 µg and Jext 300 µg solution for injection in pre-filled pen	<a href="#">Jext pre-filled pens</a>	Jext <a href="#">instructions for use</a> and <a href="#">instruction video</a>

## Anaphylaxis

1. Resuscitation Council (UK). [Emergency treatment of anaphylactic reactions](#). January 2008. Annotated with links to NICE guidance July 2012.

The Resuscitation Council recommends an intramuscular injection of adrenaline in the outer thigh to be treatment of choice for someone having an anaphylactic reaction.<sup>1</sup> Because the onset of anaphylaxis can be very fast, the individual should use an adrenaline auto-injector at the first signs of a severe reaction, then call for emergency medical help. Signs of a severe reaction include:

- swelling in the throat (altered voice, difficulty swallowing or breathing)
- wheezing
- dizziness, feeling faint, tiredness (symptoms of low blood pressure)

If in doubt about severity, or if previous reactions have been severe, the individual should use an adrenaline auto-injector. If the individual does not feel better after the first injection, the second auto-injector should be used 5–15 minutes after the first.

*Article citation: Drug Safety Update volume 11 issue 1, August 2017: 3.*

## Letters sent to healthcare professionals in July 2017

In July 2017, the following letters were sent to relevant healthcare professionals to inform them of updated safety information:

- Imbruvica ▼ (ibrutinib) and risk of hepatitis B reactivation: [hepatitis B virus status to be established before initiating treatment](#)
- Zinbryta ▼ (daclizumab): [restrictions of use of in view of fatal fulminant liver failure](#)
- Aflibercept (Zaltrap ▼) concentrate for solution for infusion 200 mg/8 mL: some batches contain previous Patient Information Leaflet; [inform patients of warnings for heart failure](#)
- Valproate medicines: only for use when no other treatment is effective or tolerated in girls, women of childbearing potential, and women who are pregnant or planning pregnancy; important actions required — [letter for specialists, specialist nurses/midwives, and general practitioners](#) and [letter for pharmacists](#)
- Shortage of Trisenox (arsenic trioxide, 1 mg/ml concentrate for solution for infusion): [replacement with imported arsenic trioxide injection 1 mg/ml \(Phenasen\) during supply shortage](#)

*Article citation: Drug Safety Update volume 11 issue 1, August 2017: 4.*

## Medical Device Alerts issued in July 2017

In this monthly update, we highlight selected Medical Device Alerts that have been issued recently by MHRA. Please note, this is not an exhaustive list of medical device alerts. For all Medical Device Alerts from MHRA, see [Alerts and recalls for drugs and medical devices](#).

A Medical Device Alert was recently issued by MHRA about:

- Haemofiltration machine: all Prismaflex systems installed with software version 6.10 – [risk of under-infusion of anticoagulant](#)

*Article citation: Drug Safety Update volume 11 issue 1, August 2017: 5.*