

# 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 3 October 2017

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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/)

In our first article this month, we feature recommended actions following reports of serious allergic reactions in patients with cows' milk allergy after injection with lactose-containing methylprednisolone (page 2). Do not use lactose-containing methylprednisolone in patients with a known or suspected allergy to cows' milk. If a patient's symptoms worsen or any new allergic symptoms occur, allergic reaction to cows' milk proteins should be suspected. Stop administration of the product and treat the patient's condition accordingly.

In our second article, we highlight the risk of central nervous system depression, including severe respiratory depression, with gabapentin (page 3). If treating patients at increased risk of these reactions, consider whether dose adjustments of gabapentin might be necessary.

Next, we inform you about rare reports of sexual dysfunction, predominantly involving erectile dysfunction and decreased libido, in some patients taking oral isotretinoin for severe acne (page 5).

In our fourth article, we remind you of the potentially fatal risk of intestinal obstruction during treatment with the antipsychotic clozapine (page 6). If constipation occurs during treatment, it is vital that it is recognised and actively treated.

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## **Methylprednisolone injectable medicine containing lactose (Solu-Medrone 40 mg): do not use in patients with cows' milk allergy**

Solu-Medrone 40 mg may contain trace amounts of milk proteins. Do not use in patients with a known or suspected allergy to cows' milk.

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

- Solu-Medrone 40 mg uses lactose produced from cows' milk as an excipient and may contain trace amounts of milk proteins; other strengths of Solu-Medrone do not contain lactose
- serious allergic reactions have been reported in patients allergic to cows' milk proteins
- do not use injectable methylprednisolone medicines that contain lactose in patients with a known or suspected allergy to cows' milk
- if a patient's symptoms worsen or any new allergic symptoms occur, allergic reaction to cows' milk proteins should be suspected; stop administration of the product and treat the patient's condition accordingly

### **European review**

Methylprednisolone is a corticosteroid with a wide variety of indications including allergic states, dermatological disease, and gastrointestinal diseases.

A recent EU review reported cases of allergic reactions, including bronchospasm and anaphylaxis, in patients allergic to cows' milk proteins treated with injectable methylprednisolone products containing lactose of bovine origin. Most patients were younger than 12 years and had childhood asthma. In some of the reported cases the adverse reaction was misinterpreted as a lack of therapeutic effect, leading to re-administration of methylprednisolone and subsequent worsening of the clinical condition of the patient.

Lactose-containing methylprednisolone medicines will be reformulated to remove any trace of milk proteins. Companies have been asked to take steps towards lactose-free formulations by 2019.

In the meantime, a [Direct Healthcare Professional Communication](#) has been sent to relevant healthcare professionals to communicate the new restriction and warnings.

### **About cows' milk allergy**

Cows' milk allergy is an adverse reaction of an immunological nature induced by cows' milk proteins. Estimates of prevalence of cows' milk allergy based on food challenge vary from 0% to 3%. Most children outgrow their allergy in early childhood and only a small proportion of patients remain allergic in adulthood.

Cows' milk allergy should be clearly distinguished from lactose intolerance, which is a non-immunologically mediated reaction to milk caused by a lack of the enzyme lactase in the small intestine, which breaks lactose from milk down into glucose and galactose.

### **Call for reporting**

Any suspected adverse reactions, including during treatment of allergic conditions, should be reported to us on a [Yellow Card](#).

### **Further information**

[Direct Healthcare Professional Communication](#). Solu-Medrone 40 mg. October 2017.

[CMDh confirms that methylprednisolone injections containing lactose must not be given to patients allergic to cow's milk proteins](#). August, 2017.

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

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### **Gabapentin (Neurontin): risk of severe respiratory depression**

Gabapentin has been associated with a rare risk of severe respiratory depression even without concomitant opioid medicines. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of central nervous system (CNS) depressants, and elderly people might be at higher risk of experiencing severe respiratory depression. Dose adjustments might be necessary in these patients.

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

- be aware of the risk of CNS depression, including severe respiratory depression, with gabapentin
- consider whether dose adjustments might be necessary in patients at higher risk of respiratory depression, including elderly people, patients with compromised respiratory function, respiratory or neurological disease, or renal impairment, and patients taking other CNS depressants
- report any suspected adverse reactions on a [Yellow Card](#)

### **Risk of respiratory depression**

A European review of gabapentin was triggered by reports of patients developing respiratory depression without concomitant use of opioids. This reaction has already been recognised with concomitant use of gabapentin with opioids (see next page).

Having considered the available evidence from worldwide spontaneous reports and in the literature, the review recommended that the product information for gabapentin should be amended to include warnings for severe respiratory depression (frequency rare; may affect up to 1 in 1,000 patients post-marketing).

## **Recommendations to minimise risk**

Dose adjustments might be necessary in patients at increased risk of experiencing this severe adverse reaction, including those:

- with compromised respiratory function or respiratory disease
- with neurological disease
- with renal impairment
- using concomitant CNS depressants
- elderly people

The patient leaflet that accompanies gabapentin is being updated to include warnings about breathing problems, which if severe may need emergency and intensive care. The leaflet advises patients to seek medical help if they experience any trouble breathing or are taking shallow breaths.

## **Reminder of risk with concomitant use of opioids**

Be aware that when prescribing gabapentin in patients who require concomitant treatment with opioid medicines, patients should be carefully observed for signs of CNS depression, such as somnolence, sedation, and respiratory depression, and the dose of either gabapentin or the opioid should be reduced appropriately.

## **UK Yellow Card Reports**

In the UK, there have been 50 Yellow Card reports of respiratory depression or dyspnoea associated with gabapentin between 19 February 1996 and 1 September 2017. Of these cases, 17 report opioids as co-suspect or concomitant medications.

## **Background**

Gabapentin (brand leader Neurontin) is an anti-epileptic drug indicated for:

- partial seizures with and without secondary generalisation
- peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults

## **Reporting of suspected adverse reactions**

Healthcare professionals are asked to report any suspected adverse reactions with gabapentin via the [Yellow Card Scheme](#).

## **Further information**

[New product information wording for Gabapentin – Extracts from PRAC recommendations on signals](#). June 2017.

*Article citation: Drug Safety Update volume 11, issue 3; October 2017: 2.*

## Isotretinoin (Roaccutane): rare reports of erectile dysfunction and decreased libido

Cases of sexual dysfunction, predominantly involving erectile dysfunction and decreased libido, have been reported rarely in patients taking oral isotretinoin for severe acne.

### Advice to healthcare professionals:

- be aware of reports of sexual side effects, including erectile dysfunction and decreased libido, in patients taking oral isotretinoin, indicated for severe acne
- the exact incidence of these adverse reactions is unknown but considering the number of patients in the UK taking the medicine, reports are understood to be rare
- report any suspected adverse reactions to isotretinoin or other medicines on a [Yellow Card](#)

### Sexual dysfunction

A routine EU review showed that some patients taking isotretinoin had reported sexual dysfunction adverse effects, including erectile dysfunction and decreased libido. One possible mechanism for this effect may be through a reduction in plasma testosterone levels.

The review recommended that sexual dysfunction including erectile dysfunction and decreased libido should be added to the list of side effects in the product information. The package leaflet for patients will include “Problems getting or maintaining an erection and lower libido” as possible side effects.

In the UK, we have received 14 Yellow Card reports of sexual dysfunction associated isotretinoin between the beginning of 1985 and 7 September 2017. In the same time period, there have been 49 reports of erectile or ejaculation dysfunction, and 23 reports of decreased or loss of libido associated with isotretinoin. We estimate that over the past few years, around 30,000 patients (male and female) per year have been treated with isotretinoin (see 2014 [Public Assessment Report](#)).<sup>1</sup>

### Reminder of risk of mood disorders

Be aware of rare reports of depression, exacerbated depression, anxiety, aggressive tendencies, mood alterations, and psychotic symptoms in association with isotretinoin treatment. Very rarely, suicidal ideation, suicide attempts, and death by suicide have been reported.

Particular care should be taken in patients with a history of depression. Monitor all patients for signs of depression and refer for appropriate treatment if necessary. Further psychiatric or psychological evaluation may be necessary after discontinuation of treatment with isotretinoin.

1. The advisory committee of the 2014 report was provided with a breakdown of the sales figures for each manufacturer of isotretinoin, however, the individual data from each manufacturer cannot be released. It is important to remember that these are estimates of usage and that precise figures on the number of patients treated cannot currently be generated due to the individual nature of each patient's treatment

## Call for reporting

The Medicines and Healthcare products Regulatory Agency continually monitors the safety of all medicines. All suspected adverse reactions, including any sexual and psychiatric adverse reactions, should be reported via the [Yellow Card Scheme](#).

## Further information

[Isotretinoin \(oral formulations\): CMDh scientific conclusions and grounds for the variation, amendments to the product information and timetable for the implementation](#). July 2017.

*Article citation: Drug Safety Update volume 11, issue 3; October 2017: 3.*

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## **Clozapine: reminder of potentially fatal risk of intestinal obstruction, faecal impaction, and paralytic ileus**

If constipation occurs during treatment with clozapine (Clozaril, Denzapine, Zaponex), it is vital that it is recognised and actively treated.

### **Advice to healthcare professionals:**

- the antipsychotic drug clozapine has been associated with varying degrees of impairment of intestinal peristalsis; this effect can range from constipation, which is very common, to very rare intestinal obstruction, faecal impaction, and paralytic ileus
- exercise particular care in patients receiving other drugs known to cause constipation (especially those with anticholinergic properties), patients with a history of colonic disease or lower abdominal surgery, and in patients aged 60 years and older
- clozapine is contraindicated in patients with paralytic ileus
- advise patients to report constipation immediately
- actively treat any constipation that occurs

## **Gastrointestinal disorders**

Clozapine has been associated with varying degrees of impairment of intestinal peristalsis. These adverse events are thought to be due to the anticholinergic properties of clozapine. The effects can range from constipation, which is very common, to intestinal obstruction, faecal impaction, and paralytic ileus, which are very rare. On a few occasions, cases have been fatal.

In the UK, there have been 370 Yellow Card reports of gastrointestinal obstruction associated with clozapine between 3 August 1993 and 11 September 2017. In this time period, there have also been 135 reports of faecaloma and 86 of paralytic ileus.

The risk of gastrointestinal adverse effects is long established with clozapine. Warnings are provided in the Summary of Product Characteristics and Patient Information Leaflet and in the BNF. However, in August 2017, a Coroner investigating a death raised concerns to the MHRA that healthcare professionals might have a lack of awareness about the risk of pseudo-obstruction or paralytic ileus and their fast onset.

### **Reminder of warnings in the product information**

Clozapine is contraindicated in patients with paralytic ileus.

When prescribing clozapine, particular care should be taken in patients at risk of constipation, including those:

- receiving medications known to cause constipation (especially those with anticholinergic properties such as some antipsychotics, antidepressants and antiparkinsonian treatments)
- with a history of colonic disease or a history of lower abdominal surgery
- aged 60 years and older

Advise patients that if they develop constipation, they should tell their doctor immediately before taking the next dose of clozapine.

It is vital that constipation is recognised early and actively treated.

Refer to the full summary product of characteristics for a complete list of warnings and recommendations for clozapine.

### **Call for reporting**

All suspected adverse reactions to antipsychotic medicines can be reported via the [Yellow Card Scheme](#).

### **Further information**

[BNF – Clozapine](#)

*Article citation: Drug Safety Update volume 11, issue 3; October 2017: 4.*

## Letters sent to healthcare professionals in September 2017

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

- [Dacogen \(decitabine\) 50 mg, powder for concentrate for solution for infusion – change in the recommendations for diluting reconstituted Dacogen solution](#)
- [Eperzan▼ \(albiglutide\): global discontinuation of medicine — do not initiate new patients; transition all current patients to an alternative therapy by July 2018](#)
- [ERWINASE from BATCH 184G\\* should be used with a 5-micron filter needle](#)
- [ReoPro \(abciximab\) 2 mg/mL solution for injection or infusion: supply shortage](#)
- [Recombinant human erythropoietins: risk of severe cutaneous adverse reactions](#)

*Article citation: Drug Safety Update volume 11, issue 3; October 2017: 5.*

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## Medical Device Alerts issued in September 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](#).

Alerts were recently issued by MHRA about:

- [All Accu-Chek® Insight insulin pumps – risk of alarm failure](#)
- [Lung ventilators: Astral 100, 100SC and 150 – potential power loss due to faulty battery](#)
- [IntelliVue patient monitors used with 12-lead ECG – risk of ECG trace distortion  
Specific models and software versions affected.](#)

*Article citation: Drug Safety Update volume 11, issue 3; October 2017: 6.*