

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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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.



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In our first article, we advise you that tapentadol may increase seizure risk in patients taking other medicines that lower seizure threshold (page 2). Read also about reports of serotonin syndrome when tapentadol is used in combination with serotonergic antidepressants.

In our second article, we issue advice for prescribers of ipilimumab, authorised for advanced melanoma, following post-marketing cases of gastrointestinal cytomegalovirus (CMV) infection or reactivation in patients reported to have corticosteroid-refractory immune-related colitis (page 4). Diagnostic work-up to exclude infectious or other causes should be performed upon presentation with diarrhoea or colitis and in patients who do not respond to steroid treatment for immune-related colitis.

Finally, read about updates made to the Yellow Card App, which you can use to report suspected adverse drug reactions (ADRs) to the MHRA and be informed of the latest safety alerts, including Drug Safety Updates. The app has new improved features to better capture safety information related to medicine exposure during pregnancy. Download the App today and let us know your thoughts (see page 6).

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Tapentadol (Palexia): risk of seizures and reports of serotonin syndrome when co-administered with other medicines

Tapentadol may increase seizure risk in patients taking other medicines that lower seizure threshold, for example, antidepressants and antipsychotics. Serotonin syndrome has also been reported when tapentadol is used in combination with serotonergic antidepressants.

Advice for healthcare professionals:

- as for all opioid medicines, tapentadol can induce seizures
- tapentadol should be prescribed with care in patients with a history of seizure disorders or epilepsy
- tapentadol may increase seizure risk in patients taking other medicines that lower seizure threshold, for example, antidepressants such as serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants, and antipsychotics
- serotonin syndrome has been reported when tapentadol is used in combination with serotonergic antidepressants (see typical presenting symptoms below)
- withdrawal of the serotonergic medicine, together with supportive symptomatic care, usually brings about a rapid improvement in serotonin syndrome
- report suspected adverse drug reactions, including those resulting from interactions between drugs, on a [Yellow Card](#)

Background

Tapentadol (Palexia) is an opioid analgesic authorised for the relief of acute moderate to severe pain that can only be adequately managed with opioid analgesics in adults and children aged 2 years and older. Tapentadol is also indicated in adults only for the management of severe chronic pain that can be adequately managed only with opioid analgesics. See the [Summary of Product Characteristics](#) for restrictions in children, including a maximum duration of use of 3 days.

Review of data for seizure risks

The risk of seizures is a recognised adverse reaction for all opioid medicines. However, a recent review of safety data for tapentadol in the EU identified the need for strengthened advice about the risk of seizures.

Approximately half of the identified spontaneous reports of seizure reflected co-administration of tapentadol with at least one other drug known to lower seizure threshold. These medicines include selective serotonin-reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and antipsychotics.

Tapentadol should be used with care in patients with a history of seizure disorders or epilepsy because of the increased risk of seizures. Strengthened warnings on seizure risk have been added to the Summaries of Product information and Patient Information Leaflets.

Reports of serotonin syndrome

We are also aware of reports of serotonin syndrome identified when tapentadol is co-administered with antidepressants, such as serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants and antipsychotics. Serotonin syndrome is likely when one of the following is observed:

- Spontaneous clonus
- Inducible or ocular clonus with agitation or diaphoresis (sweating)
- Tremor and hyperreflexia
- Hypertonia and body temperature higher than 38°C and inducible ocular clonus

Withdrawal of the serotonergic medicine together with supportive symptomatic care, usually brings about a rapid improvement. The continued use of tapentadol must be evaluated on an ongoing basis. Withdrawal symptoms can occur with abrupt cessation of treatment.

See the [Summary of Product Characteristics](#) for tapentadol for details of other interactions, including advice to avoid monoamine oxidase inhibitors with tapentadol because of the potential for hypertensive crisis.

Report any suspected adverse drug reactions

Please continue to report suspected adverse drug reactions (ADRs), including interactions between medicines, on a Yellow Card. Reporting suspected ADRs, even those known to occur in association with the medicine, adds to knowledge about the frequency and severity of these reactions and can be used to identify patients who are most at risk. Your report helps the safer use of medicines.

Healthcare professionals, patients, and caregivers can report suspected ADRs via the [Yellow Card website](#) or via the Yellow Card app. Download the app today via [iTunes Yellow Card](#) for iOS devices or via [PlayStore Yellow Card](#) for Android devices.

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Ipilimumab (Yervoy): reports of cytomegalovirus (CMV) gastrointestinal infection or reactivation

Patients on ipilimumab who present with diarrhoea or other symptoms of colitis, and those who do not respond to steroid treatment for immune-related colitis, should be investigated to exclude other causes, including infections such as cytomegalovirus (CMV). There have been post-marketing cases of gastrointestinal CMV infection or reactivation in ipilimumab-treated patients reported to have corticosteroid-refractory immune-related colitis, including fatal cases.

Advice for healthcare professionals:

- colitis occurs commonly in patients treated with ipilimumab for advanced melanoma; advise patients to contact their healthcare professional immediately at the onset of symptoms of colitis (including diarrhoea, blood in stools or abdominal pain)
- if patients on ipilimumab present with diarrhoea or colitis, investigate possible causes, including infections; perform a stool infection work-up and screen for CMV
- for patients with immune-related colitis that is corticosteroid refractory, use of an additional immunosuppressive agent should only be considered if other causes are excluded (including with screening for CMV, culture, *Clostridium difficile*, ova, and parasite) using viral PCR on biopsy, and other viral, bacterial, and parasitic causes
- report suspected adverse drug reactions associated with ipilimumab to the [Yellow Card Scheme](#)

Review of reports of gastrointestinal CMV associated with ipilimumab

Ipilimumab (Yervoy▼) is an immune checkpoint inhibitor that specifically blocks the activity of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and is authorised for advanced (unresectable or metastatic) melanoma.

A European review of spontaneous reports received up to 14 May 2018 identified a total of 40 cases worldwide suggestive of gastrointestinal-associated CMV infection or reactivation with ipilimumab monotherapy (29 cases) or ipilimumab in combination with nivolumab (11 cases).

All cases of CMV gastrointestinal infection or reactivation occurred in patients with colitis that was refractory to corticosteroid treatment. It was not possible to determine whether these patients had immune-related colitis and then developed CMV infection or reactivation due to immunosuppressant therapy, or whether CMV infection or reactivation had been initially misdiagnosed as immune-related colitis. In 30 of the 40 patients, CMV infection/reactivation was confirmed by laboratory diagnostics, including biopsy, viral load, CMV PCR, CMV antigenaemia, IgG, and IgM measurement.

Of the 40 cases, 27 cases were on treatment with ipilimumab for malignant melanoma. The gender breakdown (where specified) was 23 men and 13 women with a median age of 67 years (range 37–87 years). The time to onset from first dose of ipilimumab ranged from 18 days to 815 days (median 92 days).

Three patients died due to CMV-related colitis that was undiagnosed and then unsuccessfully treated with corticosteroids. Ten patients recovered (1 patient had sequelae), 8 patients had not recovered at the time of reporting, and 3 patients were recovering at the time of reporting.

Risk of severe diarrhoea and colitis with ipilimumab

Diarrhoea is a very common adverse drug reaction associated with ipilimumab. In clinical trials of ipilimumab 3 mg/kg monotherapy, diarrhoea and colitis of any severity were reported in 27% and 8% of patients, respectively. The frequency of severe (grade 3 or 4) diarrhoea or colitis was 5% each. The median time to onset of severe or fatal (grade 3–5) immune-related gastrointestinal reactions was 8 weeks (range 5–13 weeks) from the start of treatment. Gastrointestinal reactions can also occur when ipilimumab is used in combination with nivolumab, see the [Summary of Product Characteristics](#).

Management recommendations for diarrhoea or colitis are provided in the [Summary of Product Characteristics](#) and are based on severity of symptoms. Diarrhoea or colitis occurring after initiation of ipilimumab must be promptly evaluated to exclude infectious or other alternate causes. For severe (Grade 3 or 4) diarrhoea and immune-related colitis, ipilimumab should be permanently discontinued and systemic high-dose intravenous corticosteroid therapy initiated.

In patients with immune-related colitis who are refractory to corticosteroids, the addition of an immunosuppressive agent should only be considered if other causes have been excluded, including CMV infection or reactivation.

Report any suspected adverse drug reactions

Please continue to report any suspected adverse reactions to ipilimumab via the [Yellow Card Scheme](#). Your report will help us safeguard public health.

Article citation: Drug Safety Update volume 12, issue 6: January 2019: 2.

Yellow Card App: download the updated App to receive the latest MHRA safety news and report suspected side effects, including in pregnancy

The Yellow Card App has been updated to make it easier to use, to have useful new features, and to support reporting a suspected reaction related to medicine exposure during pregnancy. Download the App today and let us know your thoughts.

Yellow Card App

The Yellow Card App was first launched in 2015 to bring medicines safety straight to users' smartphones and has had more than 10,000 downloads to date. The App is available for download free of charge from [iTunes Yellow Card](#) for iOS devices or [PlayStore Yellow Card](#) for Android devices.

The Yellow Card App can be used to:

- Report a suspected adverse drug reaction (ADR) to a medicine, including vaccines, herbal products, and homeopathic remedies
- Stay up to date with all the latest safety information published by the MHRA, including Drug Safety Update, using the newsfeed
- Create watchlists for alerts to new safety information about your medicines of interest
- View numbers of reports received by the MHRA to specific medicines and vaccines
- View your previously sent reports as a registered user

Updated Yellow Card App

To provide an improved user experience, the Yellow Card App has undergone a major revamp. The updated App is more stable and simplifies existing features such as reporting of suspected adverse drug reactions (ADRs). The App also has easier navigation, with the ability to view newsfeed articles within the App. You can read Drug Safety Update every month this way.

New features

The updated Yellow Card App has a range of exciting new features, such as improved security, quick log in using Touch ID or Face ID, and improved news and data visualisations. The App can also be used while offline to create and save reports to send later. Registered users have access to an enhanced watchlist and view of previously submitted reports, while limited functionality is now available to guest users who can view the MHRA's general newsfeed, report a suspected ADR, and look at Yellow Card data on medicines, without needing to log in or create an account.

To support the monitoring of safety of medicines used during pregnancy, the Yellow Card app is piloting additional questions on medicine use during pregnancy. These questions will be triggered if the patient is female and of childbearing age, or where a parent is reporting a suspected adverse drug reaction in a child. You are encouraged to add information on the trimester of drug exposure, scans, previous pregnancies, use of supplements, and whether any suspected adverse effect occurred during the pregnancy. Any feedback from the pilot will be considered to further improve the questions, before being added to the Yellow Card website reporting form.

The images below show screenshots of the additional questions on medicine use during pregnancy to the App about pregnancy and an example image of the newsfeed:

Cancel **Personal Details** Save

Information about use of medicines during pregnancy are valuable to increase our knowledge of their safety - Was a pregnancy taking place at the time of the adverse reaction? *

Yes (currently pregnant) ▼

When did the exposure to the medicine occur during the pregnancy?

Please select ▼

Estimated due date ▼

Please can you provide the details of any results of scans or investigations relating to the pregnancy?

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Your feedback

Download the updated App today and try it out for yourself!

Further work is planned to continue to improve the Yellow Card App and support safety monitoring of medicines. Contact us at web-radr@mhra.gov.uk with your views and suggestions on the App and any features you would like to see added.

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Letters and drug alerts sent to healthcare professionals in December 2018

Discontinuation of Zovirax (Aciclovir) eye ointment

In December 2018, a [letter was sent to healthcare professionals](#) about the discontinuation of Zovirax (Aciclovir) eye ointment (3% w/w). The manufacturer will cease manufacture and supply of the product during 2018 due to repeated challenges in guaranteeing a sustainable product supply.

Stock of Zovirax (Aciclovir) eye ointment (3% w/w) is anticipated to continue to be available in the UK until the end of June 2019, subject to demand. There is no other branded or generic aciclovir eye ointment available. Please refer to the [UKMI memo on the discontinuation of Zovirax Eye Ointment](#) for further information on treatment options.

Recall of irbesartan/hydrochlorothiazide products

You should also be aware of the recall from pharmacies of [Actavis batches of irbesartan/hydrochlorothiazide 300/12.5mg film-coated tablets and irbesartan/hydrochlorothiazide 150/12.5mg film-coated tablets](#) as a precautionary measure due to possible contamination with N-nitrosodiethylamine (NDEA).

Advice for healthcare professionals:

- Stop supplying the [batches of irbesartan/hydrochlorothiazide listed in the alert](#) immediately. Quarantine all remaining stock and return it to your supplier using your supplier's approved process.
- If you receive queries about this issue from patients, advise them not to stop taking their medication as the health risk of discontinuing the medicine is higher than the potential risk presented by the contaminant. A treatment review is not necessary until the next routine appointment.
- We do not anticipate any shortages of Irbesartan containing products. It is possible, however, that there may be some local supply issues, in which case patients should be advised to speak to their doctor to discuss alternative treatments.

This is a developing issue and the MHRA is actively involved with the European Medicines Agency and with other medicines regulators to determine any possible impact. An investigation into other potentially impacted products is continuing and further updates will be provided as the investigation progresses. [Subscribe to MHRA drug alerts](#) for updates.

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Medical Device Alerts issued in December 2018

In this monthly update, we highlight selected Medical Device Alerts or Field Safety Notices 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](#).

In December, a Field Safety Notice was issued by Allergan to announce it was suspending sales of textured breast implants and tissue expanders and withdrawing any remaining supply in European markets.

The withdrawal decision follows a compulsory recall request from Agence Nationale de Sécurité du Médicament (ANSM), the French regulatory authority. The suspension of sales stems from the expiration of the company's CE Mark for these products. See the [Urgent Field Safety Notice for more information](#).

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