

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 12 Issue 11 June 2019

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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 that direct-acting oral anticoagulants (DOACs) are not recommended in patients with antiphospholipid syndrome because of a study showing an increased risk of recurrent thrombotic events with rivaroxaban versus warfarin in patients with triple-negative antiphospholipid syndrome and a history of thrombosis (page 2).

In our second article, we warn about cases of serious and life-threatening diabetic ketoacidosis reported in association with combination treatment with insulin and a GLP-1 receptor agonist for type 2 diabetes mellitus, particularly after rapid dose reduction or discontinuation of insulin (page 4).

Next, we communicate the withdrawal of the EU marketing authorisation for Lartruvo ▼ (olaratumab) after a clinical trial failed to show clinical efficacy in its indication of advanced soft tissue sarcoma.

On page 7, we provide information on revised and simplified pregnancy prevention educational materials for healthcare professionals and women following an in-depth European review of oral retinoid medicines (page 8).

Finally, see from pages 11 for recent letters and alerts sent to healthcare professionals about the safety of medicines and medical devices. Following our communication of temporary restrictions in the May 2019 Drug Safety Update, we highlight the letter to healthcare professionals about tofacitinib (Xeljanz ▼), which provides additional detail on the study findings that found an increased risk of pulmonary embolism with tofacitinib at an unauthorised dose of 10 mg twice-daily in patients with rheumatoid arthritis and at least one cardiovascular risk factor. We also highlight actions needed from prescribers and dispensers of Epanutin (phenytoin) 30 mg/5 ml oral suspension, which will be out of stock until late July 2019.

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Direct-acting oral anticoagulants (DOACs): increased risk of recurrent thrombotic events in patients with antiphospholipid syndrome

A clinical trial has shown an increased risk of recurrent thrombotic events associated with rivaroxaban compared with warfarin, in patients with antiphospholipid syndrome and a history of thrombosis. Other direct-acting oral anticoagulants (DOACs) may be associated with a similarly increased risk.

Advice for healthcare professionals:

- direct-acting oral anticoagulants (DOACs) are not recommended in patients with antiphospholipid syndrome, particularly high-risk patients (those who test positive for all 3 antiphospholipid tests — lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2 glycoprotein I antibodies)
- review whether continued treatment with a DOAC is appropriate for patients diagnosed with antiphospholipid syndrome, particularly high-risk patients, and consider switching to a vitamin K antagonist such as warfarin
- report suspected adverse drug reactions to DOACs on a [Yellow Card](#), including any thromboembolic events suspected to be due to lack of efficacy

Risk of recurrent thrombotic events in patients with antiphospholipid syndrome

Direct-acting oral anticoagulants (DOACs) are indicated for a variety of uses related to anticoagulation (see full indication in background). DOACs available are apixaban ([Eliquis](#)), dabigatran etexilate ([Pradaxa](#)), edoxaban ([Lixiana](#) ▼), and rivaroxaban ([Xarelto](#) ▼).

An EU review has concluded that use of DOACs in patients with antiphospholipid syndrome could be associated with increased rates of recurrent thrombotic events compared with therapy with a vitamin K antagonist.

The level of evidence for an increased risk of recurrent thrombotic events in patients with antiphospholipid syndrome differs among DOACs (see below for information for each medicine). However, there is not enough evidence that any DOAC offers sufficient protection in patients diagnosed with established antiphospholipid syndrome, particularly in patients at the highest risk for thromboembolic events (those who test positive for all 3 antiphospholipid tests – lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2 glycoprotein I antibodies).

Changes are therefore being made to the product information for these medicines to warn that use of DOACs in these patients with antiphospholipid syndrome is not recommended.

Rivaroxaban

The TRAPS study¹ was an investigator-sponsored, randomised, open-label, multicentre study with blinded endpoint adjudication. Outcomes with rivaroxaban were compared with warfarin in patients with antiphospholipid syndrome and a history of thrombosis, and at high risk for thromboembolic events (patients who persistently tested positive for all 3 antiphospholipid tests).

[Letter for healthcare professionals, May 2019.](#)

1. [Pengo V, et al. *Blood* 2018; 132: 1365–71.](#)

Clinicaltrials.gov identifier [NCT02157272](#)

The trial was terminated prematurely after the enrolment of 120 patients due to an excess of thromboembolic events among patients in the rivaroxaban arm.¹ Mean follow-up was 569 days. In the study, 59 patients were randomly assigned to rivaroxaban 20 mg (15 mg dose for patients with creatinine clearance <50 mL/min) and 61 to warfarin (INR 2.0–3.0).

Thromboembolic events occurred in 12% of patients assigned to receive rivaroxaban (4 cases of ischaemic stroke and 3 of myocardial infarction). No thromboembolic events were reported in patients assigned to receive warfarin. Major bleeding events occurred in 4 patients (7%) in the rivaroxaban group and 2 patients (3%) in the warfarin group. No deaths were reported.

Apixaban, edoxaban and dabigatran etexilate

Available data for apixaban, edoxaban and dabigatran etexilate are more limited than for rivaroxaban because there have been no completed clinical trials of these products in patients with antiphospholipid syndrome. However, available data suggest these other DOACs may be associated with a similarly increased risk of recurrent thrombotic events as with use of rivaroxaban.

Clinicaltrials.gov identifier
[NCT02295475](https://clinicaltrials.gov/ct2/show/study/NCT02295475)

One investigator-sponsored research study is ongoing to study rates of thrombosis in patients with antiphospholipid syndrome on apixaban (ASTRO-APS). The final results are not yet available.

Background

DOACs are approved for the treatment and prevention of venous thromboembolism (VTE) and prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation with one or more risk factors. Apixaban, dabigatran etexilate, and rivaroxaban are also approved for prevention of VTE in conjunction with hip or knee replacement surgery.

Rivaroxaban is also approved, in addition to acetylsalicylic acid (aspirin), for the prevention of atherothrombotic events in patients with coronary artery disease or symptomatic peripheral artery disease at high risk of ischaemic events, and in addition to acetylsalicylic acid or acetylsalicylic acid plus clopidogrel or ticlopidine, in patients after an acute coronary syndrome event with elevated cardiac biomarkers.

Report suspected adverse drug reactions with DOACs

Rivaroxaban (Xarelto ▼) and edoxaban (Lixiana ▼) are subject to additional monitoring, and so any suspected adverse drug reactions should be reported to the [Yellow Card Scheme](#). For all DOACs, serious suspected adverse drug reactions, including any cases of thromboembolic events due to lack of efficacy, should be reported on a [Yellow Card](#). Every Yellow Card report counts, and few minutes taken by you or your patient to report can make a lifetime of difference for others – so don't delay, report today!

Further information

[PRAC recommendations on signals adopted at April 2019 meeting.](#)

Article citation: Drug Safety Update volume 12, issue 11: June 2019: 1.

GLP-1 receptor agonists: reports of diabetic ketoacidosis when concomitant insulin was rapidly reduced or discontinued

Diabetic ketoacidosis has been reported in patients with type 2 diabetes on a combination of a GLP-1 receptor agonist and insulin who had doses of concomitant insulin rapidly reduced or discontinued. GLP-1 receptor agonists are not substitutes for insulin, and any reduction of insulin should be done in a stepwise manner with careful glucose self-monitoring. Abrupt discontinuation or reduction in insulin doses can lead to poor glycaemic control, with a risk of diabetic ketoacidosis.

Advice for healthcare professionals:

- serious and life-threatening cases of diabetic ketoacidosis have been reported in association with exenatide, liraglutide, and dulaglutide, particularly after discontinuation or reduction of concomitant insulin
- blood glucose self-monitoring is necessary when adjusting the dose of insulin, particularly when GLP-1 receptor agonist therapy is initiated and insulin is reduced
- if the insulin dose is to be reduced, a stepwise approach is recommended
- discuss with patients the risk factors for and signs and symptoms of diabetic ketoacidosis (see below) and advise them to seek immediate medical advice if these develop
- report suspected adverse drug reactions on a [Yellow Card](#)

Background

Exenatide ([Bydureon](#), [Byetta](#)), liraglutide ([Victoza](#), [Saxenda](#) ▼ [Xultophy](#) ▼ [combination product with insulin]), and dulaglutide ([Trulicity](#) ▼) are glucagon-like peptide-1 (GLP-1) receptor agonists (also known as GLP-1 mimetic therapies) and are authorised for use in adults with type 2 diabetes to improve glycaemic control, except for Saxenda, which is indicated for weight management.

GLP-1 receptor agonists act by stimulating insulin secretion from the pancreas in a glucose-dependent manner, as well as slowing gastric emptying and suppressing glucagon secretion. GLP-1 receptor agonists are not substitutes for insulin.

Review of cases of diabetic ketoacidosis

Serious and life-threatening cases of diabetic ketoacidosis have been reported in association with exenatide, liraglutide, and dulaglutide, particularly after rapid reduction or discontinuation of concomitant insulin. An [EU review of these reports](#) concluded that the cases could be attributed to abrupt discontinuation or dose reduction of insulin while initiating GLP-1 receptor agonist therapy, resulting in a poor glycaemic control.

This review did not identify euglycaemic diabetic ketoacidosis as a safety concern specific to treatment with GLP-1 receptor agonist therapies. A few cases in the review reported reactions suggestive of euglycaemic diabetic ketoacidosis; however, these were attributed to concomitant use of sodium-glucose co-transporter-2 inhibitor (SGLT2) medicines, which are known to be associated with euglycaemic diabetic ketoacidosis (see [Drug Safety Update April 2016](#)).

Recommendations for reducing the risk of ketoacidosis

When GLP-1 receptor agonist therapy is added to existing treatment with insulin, a reduction in the dose of insulin may be considered to reduce the risk of hypoglycaemia. A stepwise approach to insulin dose adjustment is recommended, taking into account a patient's glucose levels and individual insulin requirements.

The Summaries of Product Characteristics and Patient Information Leaflets for exenatide, liraglutide, and dulaglutide are being updated to note that a stepwise approach is recommended for insulin dose reduction and to advise that blood glucose self-monitoring is necessary when adjusting the dose of insulin, particularly during initiation of GLP-1 receptor agonist therapy.

The GLP-1 receptor agonists lixisenatide ([Lyxumia](#)) and semaglutide ([Ozempic](#)▼) are also authorised for use in the UK. Lixisenatide and semaglutide were not subject to the EU review. At the time of publication, we have not received any UK reports of diabetic ketoacidosis in association with lixisenatide and semaglutide. However, the theoretical risk of diabetic ketoacidosis when changes are made to insulin dose cannot be excluded.

Characteristics of reactions reported

Up until the end of May 2019, the MHRA's Yellow Card Scheme has received 26 reports of diabetic ketoacidosis, and 10 reports of reactions relating to ketone body formation (increased blood ketones, ketonuria) in patients taking exenatide, liraglutide, and dulaglutide. This corresponds to a UK estimated exposure to these 3 medicines of about 2 million patient-years of treatment between 2007 and 2018.¹

In around a third of the UK cases reported, insulin was either discontinued or the dose was rapidly reduced at initiation of the GLP-1 receptor agonist. In the remaining cases, it is difficult to establish the role of these agents due to possible precipitating factors for diabetic ketoacidosis, such as other medicines or underlying conditions.

Although nausea and vomiting may be considered adverse drug reactions of GLP-1 receptor agonists, these are also well-known symptoms of diabetic ketoacidosis and should be taken seriously when initiating GLP-1 receptor agonists and adjusting insulin doses.

Many of the cases of diabetic ketoacidosis and related reactions occurred within 2 weeks of initiation of GLP-1 receptor agonists. Nausea and vomiting were commonly co-reported reactions.

Signs and symptoms of diabetic ketoacidosis

Inform patients of the signs and symptoms of diabetic ketoacidosis (nausea, vomiting, abdominal pain, excessive thirst, increased frequency of urination, difficulty breathing, confusion, unusual fatigue, or sleepiness) and the need for urgent medical attention if they occur.

1. Data derived from IQVIA MIDAS Q1 2006 to Q4 2018, by the MHRA, March 2019. Patient-years estimated from the data by using defined daily doses (DDD) as provided by WHO.

Report suspected adverse drug reactions on a Yellow Card

Please continue to report suspected adverse drug reactions (ADRs) associated with GLP-1 receptor agonists 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.

Further information

[PRAC recommendations on signals. Adopted at the 26-29 November 2018 PRAC meeting.](#)

Article citation: Drug Safety Update volume 12, issue 11: June 2019: 2.

Lartruvo ▼ (olaratumab): withdrawal of the EU marketing authorisation due to lack of efficacy

The ANNOUNCE study failed to show clinical efficacy for olaratumab in its current indication of advanced soft tissue sarcoma and the benefit risk balance is therefore now considered negative. No new patients should be started on olaratumab therapy.

Advice for healthcare professionals:

- the ANNOUNCE phase 3 study (an EU regulatory requirement) to assess olaratumab (Lartruvo ▼) in combination with doxorubicin in patients with advanced or metastatic soft tissue sarcoma failed to show a clinical benefit
- the benefit-risk balance of olaratumab is therefore negative and the marketing authorisation in the EU will be withdrawn
- do not start new patients on olaratumab
- for patients currently on treatment, consider alternative treatment options since available stock will expire by April 2020
- continue to report any suspected adverse reactions to black triangle medicines to the [Yellow Card Scheme](#)

Background

Olaratumab was authorised in the European Union in November 2016 to treat advanced soft tissue sarcoma. At time of its approval, data on the effects of olaratumab were limited due to the small number of patients included in the main study that supported the conditional authorisation as an orphan drug. The medicine was therefore granted a marketing authorisation on condition that the company provided additional data from the ANNOUNCE study to confirm the efficacy and safety of the medicine.

ANNOUNCE study findings

The ANNOUNCE study did not show clinical benefit of olaratumab in combination with doxorubicin compared with doxorubicin, a standard of care treatment for advanced soft tissue sarcoma. Specifically, the study of 509 patients (258 in the investigational arm and 251 in the control arm) did not meet the primary endpoint to prolong overall survival in the study (hazard ratio 1.05; 95% CI 0.84–1.30; median overall survival 20.4 months for the olaratumab plus doxorubicin group versus 19.8 months for the doxorubicin group).

Overall survival was also not prolonged by olaratumab in the subpopulation of 234 patients with leiomyosarcoma (119 in the investigational arm and 115 in the control arm; hazard ratio 0.95, 95% CI 0.690–1.312; median overall survival 21.6 months for the olaratumab plus doxorubicin group versus 21.9 months for the doxorubicin group).

There was no clinical benefit for key secondary efficacy endpoints, including median progression-free survival in the overall population (hazard ratio 1.23, 95% CI 1.009–1.502; median progression-free survival 5.4 months for the olaratumab plus doxorubicin group versus 6.8 months for the doxorubicin group).

No new safety concerns were identified in the study. Because this study did not show a clinical benefit, the conditional marketing authorisation for olaratumab will be withdrawn.

[Letter sent to healthcare professionals.](#)

Report suspected adverse drug reactions via the Yellow Card Scheme

Please continue to report any suspected adverse drug reaction via the Yellow Card Scheme, even if the suspect drug no longer has a marketing authorisation.

Healthcare professionals, patients, and caregivers can report suspected side effects via the [Yellow Card website](#) or via the Yellow Card App available from [Apple App Store](#) and [Google Play Store](#).

You can also use the app to access the latest safety information from the MHRA about medicines and medical devices on the Newsfeed. Search for medicines to see details of Yellow Card reports others have made. Medicines of interest to you can also be added to a Watch List to receive news and alerts about new side effects and safety advice as it emerges.

Article citation: Drug Safety Update volume 12, issue 11: June 2019: 3.

Oral retinoid medicines ▼ : revised and simplified pregnancy prevention educational materials for healthcare professionals and women

New prescriber checklists, patient reminder cards, and pharmacy checklists are available to support the Pregnancy Prevention Programme in women taking acitretin, alitretinoin, and isotretinoin. Advice about the risk of neuropsychiatric reactions has been made consistent for all oral retinoid medicines.

Advice for healthcare professionals about teratogenicity:

- following a detailed review, educational materials to support the Pregnancy Prevention Programme for the oral retinoid medicines acitretin, alitretinoin, and isotretinoin have been revised and simplified
- due to a high risk of serious congenital malformations, these medicines must not be used in pregnancy, and any use in women and girls must be within the conditions of a Pregnancy Prevention Programme, which are consistent with those previously in place (see below)

Advice for healthcare professionals about neuropsychiatric reactions:

- advice about a possible risk of neuropsychiatric reactions has been made consistent for oral retinoid medicines (acitretin, alitretinoin, bexarotene, isotretinoin, and tretinoin)
- monitor any patients treated with an oral retinoid for signs of depression or suicidal ideation and refer for appropriate treatment, if necessary; particular care needs to be taken in patients with history of depression
- advise patients taking an oral retinoid that they may experience changes in their mood or behaviour and that they should speak to their doctor if their mood is affected; they should be encouraged to let family and friends know they are taking an oral retinoid so they can look out for any change in mood
- report any suspected adverse drug reactions to retinoid medicines to the [Yellow Card Scheme](#)

Background

Retinoid-containing medicinal products are available in oral and topical forms. An [EU in-depth review](#) of all the available data on safety and efficacy for all retinoid medicines concluded that the balance between benefits and risks for retinoids remains favourable. The review recommended that educational materials for patients and healthcare professionals about pregnancy prevention measures should be simplified and made consistent and warnings about neuropsychiatric disorders harmonised across oral retinoid medicines (see [EMA Public Assessment Report](#)).

Review of the effectiveness of pregnancy prevention measures

Revised and simplified educational materials

Women and girls of childbearing potential taking oral retinoids to treat dermatological conditions must be supported by a Pregnancy Prevention Programme.

The retinoid medicines that have a Pregnancy Prevention Programme as a condition of the licence are oral isotretinoin ([Roaccutane](#) ▼) for severe acne, oral acitretin ([Neotigason](#) ▼) for severe psoriasis, and oral alitretinoin ([Toctino](#) ▼) for chronic severe hand eczema. The regulatory requirement for a Pregnancy Prevention Programme has been in place for female patients taking these oral retinoids since 2005.

The requirements of the Pregnancy Prevention Programme have not changed. Educational materials to support healthcare professionals and female patients using acitretin, alitretinoin, and isotretinoin have been simplified and are now consistent, irrespective of which brand of medicine a patient receives. The educational materials are:

Educational materials are available at <https://www.medicines.org.uk/emc>

- prescriber checklist – to be used by the dermatologist, specialist dermatology nurse, or a prescribing GP with a special interest in dermatology to record the discussion of risks with the patient. A copy should be provided to the patient
- patient card – to be given by the dermatologist, specialist dermatology nurses, or prescribing GP to reinforce the key safety messages around risks
- pharmacist checklist – to be used as an aide memoire by pharmacists when dispensing oral retinoid medicines

New educational materials are available in electronic format at <https://www.medicines.org.uk/emc> and hardcopy distribution is ongoing to dermatology clinical teams, including consultant dermatologists, and to hospital pharmacists.

[Letter to healthcare professionals.](#)

Reminder of pregnancy testing requirements

The terms of the Pregnancy Prevention Programme include that female patients at risk of pregnancy should receive regular follow-up and pregnancy testing, depending on method of contraception and pregnancy risk. The regulatory advice for pregnancy testing requirements of oral retinoids is displayed in the table below. Ideally pregnancy testing should be done on the same day as the issuing and dispensing of the prescription. The dates and results of pregnancy tests should be documented in the medical notes.

Oral retinoid medicine	Pregnancy testing advice <u>before</u> therapy	Pregnancy testing advice <u>during</u> therapy	Pregnancy testing advice <u>after</u> therapy
Acitretin (Neotigason ▼)	Up to 3 days before the first dose is given	Ideally monthly, according to risk of pregnancy*	1–3 monthly intervals for 3 years after stopping treatment
Alitretinoin (Toctino ▼)	Shortly before first prescription (preferably a few days)	Ideally monthly, according to risk of pregnancy*	1 month after stopping treatment
Isotretinoin (Roaccutane ▼)	Shortly before first prescription (preferably a few days)	Ideally monthly, according to risk of pregnancy*	1 month after stopping treatment

*The need for repeated medically supervised pregnancy tests every month should be determined according to local practice including consideration of the patient's sexual activity, recent menstrual history (abnormal menses, missed periods or amenorrhoea), and [method of contraception](#).

Teratogenic risk with topical retinoids

Systemic exposure is thought to be negligible following application of topical retinoids (topical adapalene, alitretinoin, isotretinoin, tazarotene, and tretinoin) during pregnancy. However, since risk cannot be excluded, use of topical retinoids is contraindicated during pregnancy as a precaution. Women and girls should be advised not to use topical retinoids if they are planning a pregnancy and to use effective contraception to minimise the risk of accidental exposure in pregnancy if they are of childbearing potential.

Oral retinoids indicated for haematological malignancies

Oral tretinoin ([Vesanoid](#)) is authorised for promyelocytic leukaemia. Oral bexarotene ([Targretin](#)) is authorised for T-cell lymphoma. These two products do not have a Pregnancy Prevention Programme in light of their oncology indication and specialist care setting. However, they are extremely teratogenic and the Summaries of Product Characteristics for these medicines should be consulted for contraceptive and pregnancy testing requirements in female patients at risk of pregnancy.

Review of risk of neuropsychiatric disorders

Harmonised warnings and advice

Evidence for a possible link between isotretinoin and psychiatric disorders (for example, depression, suicidal behaviour) has been under review for many years. The MHRA has monitored reports closely and since 2015 advice has been present in the Patient Information Leaflet for isotretinoin that patients should discuss any history of mental illness with their doctor before taking isotretinoin.

Cases of newly diagnosed depression, worsening of existing depression, and anxiety have been reported with oral retinoids. The limitations of the available data did not allow the review to establish a clear causal association between risk of neuropsychiatric disorders and use of oral retinoids. However, patients with severe skin conditions may be more likely to develop neuropsychiatric disorders due to the nature of the disease. The review therefore concluded that the prescribing information for oral retinoids should include a warning to ensure patients are informed about the possible risk and what to do if symptoms occur (see [EU Public Assessment Report](#)).

Therefore, advice about monitoring for neuropsychiatric disorders has been made consistent for alitretinoin and isotretinoin products, and added to the product information for acitretin, tretinoin and bexarotene.

Advice about monitoring for neuropsychiatric disorders

All patients treated with an oral retinoid should be monitored for signs of depression or suicidal ideation and refer for appropriate treatment, if necessary. Particular care needs to be taken in patients with history of depression.

Healthcare professionals should discuss with patients taking an oral retinoid that they may experience changes in their mood or behaviour and to talk to their doctor if their mood is affected. Patients should also be encouraged to let family and friends know they are taking an oral retinoid so they can look out for any change in mood.

Topical retinoids and neuropsychiatric disorders

For topical retinoids (adapalene, alitretinoin, isotretinoin, tazarotene, and tretinoin), the review concluded that data show systemic exposure is negligible following topical application and is unlikely to be associated with an increased risk of neuropsychiatric disorders (see [EU Public Assessment Report](#)).

Report suspected adverse drug reactions

Please continue to report any suspected adverse drug reactions (ADRs) associated with retinoid medicines to the MHRA through the Yellow Card Scheme. It is easiest and quickest to report ADRs online via the [Yellow Cards website](#) or via the Yellow Card app available from [Apple App Store](#) and [Google Play Store](#).

See article in the [January 2019 Drug Safety Update](#) for how you can use the Yellow Card App to report ADRs linked to exposure of medicines in pregnancy.

Article citation: Drug Safety Update volume 12, issue 11: June 2019: 4.

Letters and drug alerts sent to healthcare professionals in May 2019

Tofacitinib (Xeljanz▼): letter to provide additional detail on safety concerns

In the [May 2019 Drug Safety Update](#), we informed you that following observation in a clinical study of an increased risk of pulmonary embolism and overall mortality associated with tofacitinib at the unauthorised dose of 10 mg twice-daily in rheumatoid arthritis, a safety review has started and new restrictions introduced.

A [letter has now been sent to healthcare professionals](#) to provide more detail on the preliminary results of the study upon which this advice was based.

Epanutin (phenytoin) oral solution shortage – letter and alert

Epanutin (phenytoin) 30 mg/5 ml oral suspension will be out of stock from the week commencing 10 June 2019 until late July 2019.

All healthcare professionals who prescribe, dispense, or administer Epanutin oral suspension should consult the [supply disruption alert](#) issued by the Department of Health & Social Care (DHSC) on 6 June 2019.

Pfizer have obtained permission from the MHRA to import Canadian stock as an unlicensed product, branded as Dilantin (phenytoin) 30 mg/5 ml oral suspension – see [letter to healthcare professionals](#).

There are small differences in the excipients: Dilantin-30 oral suspension contains amaranth (E123), whereas Epanutin oral suspension contains carmoisine (E122).

No dosing adjustments are necessary but the Patient Information Leaflet (PIL) for [Canadian Dilantin-30](#) oral suspension contains different dosing information compared to the Epanutin PIL. Patients should be counselled to remain on their prescribed dosing regimen of phenytoin and the need to consult their doctor if they are unsure.

Alternative phenytoin formulations (other than Dilantin 30mg/5ml oral suspension) are not directly interchangeable. Switching between alternative formulations may require specialist advice, support, or referral – see [Drug Safety Update for advice about equivalence of antiepileptic drugs](#).

Other letters to healthcare professionals

- [Trisenox \(arsenic trioxide, 1 mg/ml concentrate for solution for infusion\): replacement with import of arsenic trioxide injection 1 mg/ml \(Phenasen\) into the UK during the supply shortage](#)
- [Lapatinib \(Tyverb\): important update to the therapeutic indication and Summary of Product Characteristics](#)
- [Apixaban \(Eliquis\), dabigatran etexilate \(Pradaxa\), edoxaban \(Lixiana▼\) and rivaroxaban \(Xarelto▼\) are not recommended in patients with antiphospholipid syndrome due to possible increased risk for recurrent thrombotic events](#)
- [Lartuvo▼ \(olaratumab\): withdrawal of the EU marketing authorisation due to lack of therapeutic efficacy](#)

Other alerts

[Company led drug alert - Macopharma intravenous infusion bags](#). Issued 7 May 2019. Macopharma is recalling certain batches of intravenous infusion bags as a precaution. This is due to the detection of metal particles in two infusion bags. See [list](#) in alert for recalled products, which include sodium chloride, glucose, and ringer lactate infusions.

[Class 2 Medicines Recall: Co-amoxiclav 125 mg/31.25 mg/5 ml and 25 mg/62.5 mg/5 ml Powder for Oral Suspension \(MDR 24-05/19\)](#). Issued 13 May 2019. A potential packaging problem relating to poor seal adherence could cause clumping of the powder within the bottle. Remaining stocks of the impacted batches should be quarantined and returned to the original supplier.

For the latest alerts, including those from June 2019, see [Alerts and recalls for drugs and medical devices](#).

Article citation: Drug Safety Update volume 12, issue 11: June 2019: 5.

Medical Device Alerts issued in May 2019

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](#).

- [Recommendations for ongoing use of paclitaxel drug coated balloons \(DCBs\) and implantable drug-eluting stents \(DESs\) in the treatment of patients with peripheral artery disease \(PAD\) \(MDA/2019/023\)](#). Issued 4 June 2019. Recommendations are in place following concerns over an increase in patient mortality from 2 years after treatment. Paclitaxel drug coated balloons (DCBs) or drug-eluting stents (DESs) are not to be used in the routine treatment of patients with intermittent claudication until further notice.
- [Aisys and Aisys CS2 anaesthesia devices with Et Control option and software versions 11, 11SP01 and 11SP02 – risk of patient awareness due to inadequate anaesthesia \(MDA/2019/022\)](#). Issued 30 May 2019. Manufactured by GE Healthcare – device may fail to deliver the set agent concentration in End Tidal Control mode.

Article citation: Drug Safety Update volume 12, issue 11: June 2019: 6.
