

# 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

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## Contents

<b>Yellow fever vaccine (Stamaril) and fatal adverse reactions: extreme caution needed in people who may be immunosuppressed and those 60 years and older</b>	page 2
<b>Valproate medicines and serious harms in pregnancy: new Annual Risk Acknowledgement Form and clinical guidance from professional bodies to support compliance with the Pregnancy Prevention Programme</b>	page 5
<b>Belimumab (Benlysta ▼): increased risk of serious psychiatric events seen in clinical trials</b>	page 7
<b>Pregabalin (Lyrica), gabapentin (Neurontin) and risk of abuse and dependence: new scheduling requirements from 1 April 2019</b>	page 9
<b>Elvitegravir boosted with cobicistat: avoid use in pregnancy due to risk of treatment failure and maternal-to-child transmission of HIV-1</b>	page 12
<b>Letters and drug alerts sent to healthcare professionals in March 2019</b>	page 14
<b>Medical Device Alerts issued in March 2019</b>	page 15

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, following 2 recent reports of fatal adverse reactions, we remind healthcare professionals of the need for careful and individualised benefit–risk assessment before administering the yellow fever vaccine (page 2). The vaccine must not be given to a patient with a history of thymus dysfunction or who is immunosuppressed, and extreme caution should be used in people aged 60 years and older due to the substantially increased risk of serious adverse reactions.

Compliance with the Valproate Pregnancy Prevention Programme remains a concern and to support healthcare professionals to reduce and ultimately eliminate use of valproate in pregnancy, we provide a revised Annual Risk Acknowledgement Form and highlight clinical guidance from healthcare professional bodies (page 5).

On page 7, read of clinical trial findings, including recent interim results from a randomised trial, showing an increased risk of depression, suicidal ideation or behaviour, or self-injury in patients with systemic lupus erythematosus receiving belimumab compared with those receiving placebo.

Next, we remind you of the risk of abuse and dependence with pregabalin and gabapentin and your changing legal responsibilities in accordance with new prescribing and dispensing controls, which came into force on 1 April 2019 (page 9).

On page 12, read of recent pharmacokinetic data showing exposure of elvitegravir boosted with cobicistat (Genvoya ▼, Stribild) to be lower during the second and third trimesters of pregnancy than postpartum. Although no cases of mother-to-child transmission have been recorded, the potential risk of treatment failure means elvitegravir/cobicistat should not be used for the treatment of HIV in pregnancy.

Finally, see page 14 for recent letters and alerts, including important advice for prescribers of tofacitinib, indicated for rheumatoid arthritis and ulcerative colitis.

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## **Yellow fever vaccine (Stamaril) and fatal adverse reactions: extreme caution needed in people who may be immunosuppressed and those 60 years and older**

We have recently received 2 reports of fatal adverse reactions to the yellow fever vaccine (Stamaril). Due to an increased risk of life-threatening reactions, the vaccine must not be given to anyone with a medical history of thymus dysfunction or who is immunosuppressed. In addition, extreme caution must be used and a careful risk assessment conducted before vaccination of people aged 60 years and older due to a substantially increased risk of such adverse reactions in this age group.

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

- as with any live attenuated vaccine, yellow fever vaccine must not be given to people who may be immunosuppressed
- yellow fever vaccine is contraindicated in people with a history of thymus dysfunction (including myasthenia gravis and thymoma)
- yellow fever vaccine is contraindicated in people who have had their thymus gland removed (thymectomy)
- in people aged 60 years and older, the vaccine should only be given when it is considered that there is a significant and unavoidable risk of acquiring yellow fever infection
- professionals who administer yellow fever vaccine must be familiar with any contraindications and special precautions before proceeding with immunisation.
- if there is any doubt as to whether a person who is due to receive yellow fever vaccine may be immunosuppressed, immunisation should be deferred until specialist advice has been sought
- protocols and checklists should be strengthened to avoid inappropriate administration that can lead to severe and possibly fatal adverse effects; those administering the vaccine should also be familiar with the [YF Vaccine Centre code of practice](#)
- any suspected adverse reactions during immunisations should be reported on a [Yellow Card](#)

### **Background**

We previously issued advice (see [April 2016 Drug Safety Update](#), and a reminder in [November 2017 Drug Safety Update](#)) that live attenuated vaccines should not be given to people who are clinically immunosuppressed (either due to therapy, underlying illness, or pregnancy). This is because live vaccine strains can replicate and cause an extensive, severe, and sometimes fatal infection.

### **Recent reports of fatal adverse reactions to yellow fever vaccine**

In recent months, we have been notified of 2 fatal adverse reactions to yellow fever vaccine. In one case, the vaccine was given to a person with a history of thymectomy following a thymoma (a contraindication in the product information). In another case, the vaccine was given to a 67-year-old with no other known risk factors. Both patients died shortly after vaccination due to suspected yellow fever vaccine-associated viscerotropic disease (YEL-AVD).

YEL-AVD is a recognised adverse reaction that resembles severe yellow fever infection. The global reporting rate is around 1 case in every 1 million people vaccinated, with thymus disease, immunosuppression, and an age of 60 years and older increasing the risk.<sup>1,2,3</sup> Another serious risk of vaccination is yellow fever vaccine-associated neurotropic disease (YEL-AND), which can occur at a similar rate and with the same risk factors. YEL-AND can present with a variety of neurological manifestations.

1. Thomas RE. [Drug Des Devel Ther](#) 2016; 10: 3345–53.

2. Lindsey N, et al. [J Travel Med](#) 2016; 23: taw045.

3. Rafferty E, et al. [Vaccine](#) 2013; 31: 5798–805.

### **Contraindications and warnings for the yellow fever vaccine**

For full prescribing information and warnings, precautions, and risks, please refer to the [Summary of Product Characteristics](#).

Yellow fever vaccine is contraindicated in any person who is immunosuppressed due to immunosuppressive therapy or congenital or idiopathic disease. This includes a history of thymus dysfunction (including myasthenia gravis and thymoma). A history of thymectomy is also a contraindication.

Due to a higher risk of severe and potentially fatal adverse reactions, yellow fever vaccine should only be given to people aged 60 years and older when it is considered that there is a significant and unavoidable risk of acquiring yellow fever infection.

Any healthcare professional prescribing or administering the vaccine must ensure they are fully familiar with the up-to-date [Summary of Product Characteristics](#). More information and guidance on yellow fever vaccine can also be found in [the Green Book](#) and the [National Travel Health Network and Centre \(NaTHNaC\) website](#).

We are in the process of reviewing the benefit-risk balance of yellow fever vaccine and measures to minimise risks in the light of these cases and the latest scientific data. The [Commission on Human Medicines](#) has convened an Expert Working Group, which will make recommendations. We will update guidance, as necessary.

### **Risk assessment at vaccination**

When a person presents for yellow fever immunisation, it is important that healthcare professionals clearly discuss with them the individual risks and benefits of the vaccine based on their specific travel itinerary.

Sufficient time should be set aside to ensure that the person is immune competent and has no contraindications to the vaccine, including a review of full medical history and any available medical records. Any potential history of thymus disease or thymus removal should be specifically queried. Any decision to administer the vaccine to a person aged 60 years and older must be based on a significant and unavoidable risk of acquiring yellow fever infection.

Provision of the [Patient Information Leaflet](#) would provide a helpful basis for this discussion with potential vaccinees. Risk assessment checklists should also be used to ensure checks have been completed and patients have been assessed for immunocompetence (in line with local and organisational requirements).

NaTHNaC recommends that health professionals use a travel risk assessment form to guide the travel health consultation and, where appropriate, seek specialist advice when a significant medical history is identified. More information on yellow fever, and the YF Vaccine Centre code of practice can be found on the [NaTHNaC website](#).

**Report suspected adverse reactions to vaccines or medicines**

Please continue to report suspected adverse reactions to vaccines and other medicines to the [Yellow Card Scheme](#). When reporting a suspected reaction to a vaccine, please provide the brand name (or product licence number and manufacturer) and the specific batch number.

Any medication error (for example, vaccination of a contraindicated patient) that results in harm should be reported via the [Yellow Card Scheme](#). Medication errors in the absence of harm should be reported to NHS England via the [National Reporting and Learning System](#).

*Article citation: Drug Safety Update volume 12, issue 9: April 2019: 1.*

## **Valproate medicines and serious harms in pregnancy: new Annual Risk Acknowledgement Form and clinical guidance from professional bodies to support compliance with the Pregnancy Prevention Programme**

Ongoing patient survey data suggest that more effort is needed by clinicians to achieve full and timely compliance with the valproate Pregnancy Prevention Programme and meet the goal to rapidly reduce and eventually eliminate the harms of valproate in pregnancy in view of its serious teratogenicity.

We have updated the Annual Risk Acknowledgement Form, which should be used during annual specialist review of all women and girls of childbearing potential on valproate medicines (irrespective of indication). Specialists should comply with guidance given on the form if they consider the patient is not at risk of pregnancy, including the need for regular review in case her risk status changes.

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

- use the revised [Annual Risk Acknowledgement Form](#) (version dated March 2019) at initiation and annual review of all girls and women of childbearing potential on valproate medicines (irrespective of indication)
- specialists should comply with guidance on the form if they consider there to be compelling reasons to indicate their patient is not at risk of pregnancy, including the need to document reasons for this and for the patient or responsible person to sign to confirm these are correct
- if the absence of pregnancy risk may change (for example, the patient is pre-menarchal), the date for the next annual discussion of the risks must be documented and the patient or the patient's family or caregivers asked to contact the prescriber rapidly if the situation changes
- there is no safe dose of valproate that can be used in pregnancy – see reminder below for key facts about the risks if pregnancies are exposed to valproate

### **Revised Annual Risk Acknowledgement form**

Children exposed to valproate in utero have a very high risk for congenital malformations (10% risk) and neurodevelopmental disorders (30–40% risk). It is the prescriber's responsibility to ensure women and girls of childbearing potential (from menarche to menopause) who are taking a valproate medicine, irrespective of indication, fulfil all the [requirements of the Pregnancy Prevention Programme](#). These responsibilities include that the patient (or responsible person) and their specialist must complete the Annual Risk Acknowledgement Form at each year's annual review.

See [Drug Safety Update April 2018](#)

Download the form at <https://www.gov.uk/guidance/valproate-use-by-women-and-girls>

The [Annual Risk Acknowledgement Form](#) has been updated following feedback from healthcare professionals and stakeholders and should be used for all future reviews of female patients on valproate.

The form can now be used to record when the specialist considers the patient not to be at risk of pregnancy, either permanently or until the date of the next annual review. Patients or their responsible person must countersign this section to confirm details given are correct. [Download the revised Annual Risk Acknowledgement Form now.](#)

## NICE guidance summary

To support healthcare professionals to understand their clinical responsibilities for valproate, NICE has produced a [summary of their guidance and safety advice](#).

## Pan-college guidance

Experts from 13 national healthcare bodies, including 7 Royal Colleges, have produced [clinical guidance to support healthcare professionals](#) involved in the care of women on valproate. The 'pan-College' guidance advises on the more challenging issues that clinicians across primary and specialist care might encounter in daily practice. These include transition from paediatric to adult services, competence to consent to treatment, and confidentiality.

## Paediatric guidance

The British Paediatric Neurology Association (BPNA) and the Royal College of Paediatrics and Child Health (RCPCH) have developed [joint guidance to provide recommendations about the use of valproate in female patients under 18 years of age](#).

### Reminder of key facts about the risks of valproate in pregnancy

- 1 in 10 babies (10%) exposed to valproate in pregnancy are born with a congenital malformation – for the general population, the risk is about 2–3%<sup>1</sup>
- Folic acid supplementation may decrease the general risk of neural tube defects but there is evidence that it does not reduce the risk of birth defects associated with valproate exposure
- There is no safe dose of valproate that can be used in pregnancy – in a comparative study, all doses of valproate increased the risk of major congenital malformations<sup>2</sup>
- Around 3 to 4 in 10 children (30–40%) exposed to valproate in pregnancy have delays in their development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding), and memory problems<sup>3</sup>
- IQ in school-aged children (age 6 years old) with a history of valproate exposure in pregnancy was recorded to be on average 7–10 points lower than children exposed to other antiepileptic drugs<sup>4</sup>
- Children with a history of valproate exposure in pregnancy have a 3-fold risk of autistic spectrum disorder and 5-fold risk of childhood autism compared with general population<sup>5</sup>
- Children exposed to valproate in pregnancy may be at increased risk of attention deficit/hyperactivity disorder (ADHD)<sup>6</sup>

1. Weston J, et al. [Cochrane Database Syst Rev](#) 2016; 11: CD010224.

2. Thompson, et al. [Lancet Neurol](#) 2018; 17: 530–38.

3. Bromley RL, et al. [Epilepsia](#) 2010; 51: 2058–65.

4. Meador KJ, et al. [Lancet Neurol](#) 2013 12: 244–52.

5. Christensen J et al. [JAMA](#) 2013; 309: 1696–703.

6. Cohen MJ et al. [Epilepsy Behav](#) 2011; 22: 240–246.

Article citation: *Drug Safety Update* volume 12, issue 9: April 2019: 2.

## **Belimumab (Benlysta ▼): increased risk of serious psychiatric events seen in clinical trials**

Clinical trials, including interim findings from a randomised trial, show an increased risk of depression, suicidal ideation or behaviour, or self-injury in patients with systemic lupus erythematosus receiving belimumab compared with those receiving placebo in addition to standard therapy. Assess patients for these risks before the start of treatment with belimumab and advise them to promptly seek medical attention if they develop new or worsening depression, suicidal ideation or thoughts about injuring themselves.

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

- an increased risk for serious psychiatric events (depression, suicidal ideation or behaviour [including death by suicide], or self-injury) has been observed in patients receiving belimumab from clinical trials, including recent interim findings from a randomised trial
- carefully assess the risk of depression and suicide, considering the patient's medical history and current psychiatric status, before belimumab is started
- monitor all patients for new or worsening signs of these risks during treatment
- in patients with new psychiatric symptoms or if existing psychiatric symptoms worsen, assess the benefits and risks of continuing treatment
- report any suspected adverse reactions, including alterations of mood, associated with belimumab to the [Yellow Card Scheme](#)

### **Advice to give to patients (and caregivers if appropriate):**

- people taking belimumab may experience changes in their mood or behaviour, and should promptly seek medical attention if they experience new or worsening depression, suicidal ideation, or thoughts about injuring themselves
- patients may wish to let family and friends know they are taking belimumab so they can look out for any changes in mood

### **Risk of suicidal thoughts and behaviour**

An imbalance in rates of psychiatric events was observed in the clinical studies that led to the approval of belimumab. Assessment found the benefits of belimumab to outweigh the risks. However, as a condition of its licence, the marketing authorisation holder for belimumab was requested by regulators to conduct a randomised, placebo-controlled clinical trial ([BEL115467](#)) to evaluate all-cause mortality and pre-specified adverse events of special interest, including selected serious psychiatric events. The study is global and currently ongoing.

1-year data from this study show that, compared with patients who received placebo plus standard therapy, more patients who received belimumab plus standard therapy reported events of serious depression and suicidal ideation or behaviour or self-injury (see table).

[Letter to healthcare professionals, March 2019.](#)

Prescribers are therefore advised to carefully assess the risk of depression and suicide, considering the patient's medical history and current psychiatric status, before belimumab is started and to advise patients to seek medical attention if they experience new or worsening psychiatric symptoms.

**Table: Patients reporting serious depression or suicidality (as-treated population, study BEL115467)**

	Placebo (N=2001)	Belimumab IV 10 mg/kg (N=2002)
Number of patients reporting serious depression*	1 (<0.1%)	7 (0.3%)
Number of patients reporting suicidal ideation or behaviour or self-injury*	5 (0.2%)	15 (0.7%)

\*As per study investigator report

### About belimumab

[Belimumab](#) is a human IgG1 $\lambda$  monoclonal antibody, specific for soluble human B-lymphocyte stimulator protein. Belimumab is authorised for the treatment, as add-on therapy, of adults with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (for example, positive anti-dsDNA and low complement) despite standard therapy. In 2018 the UK estimated exposure to belimumab was 102 patient-years.<sup>1</sup>

1. Data derived by MHRA, in March 2019, from IQVIA MIDAS 2018. Patient-years estimated by using defined daily doses (DDD) as provided by WHO.

### Report suspected adverse drug reactions via the Yellow Card scheme

As for all medicines, MHRA will continue to monitor the benefit and risks of belimumab. Please continue to report any suspected adverse drug reaction via the Yellow Card Scheme. Remember only a suspicion is needed to report – if in doubt, please complete a Yellow Card.

Healthcare professionals, patients, and caregivers can report suspected side effects 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.

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 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 9: April 2019: 3.*



## **Pregabalin (Lyrica), gabapentin (Neurontin) and risk of abuse and dependence: new scheduling requirements from 1 April**

As of 1 April 2019, pregabalin and gabapentin are controlled under the Misuse of Drugs Act 1971 as Class C substances and scheduled under the Misuse of Drugs Regulations 2001 as Schedule 3. Evaluate patients carefully for a history of drug abuse before prescribing pregabalin and gabapentin and observe patients for development of signs of abuse and dependence.

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

- to reflect growing concern about abuse, both pregabalin and gabapentin are now classified as Class C controlled substances (under the Misuse of Drugs Act 1971) and scheduled under the Misuse of Drugs Regulations 2001 (as amended) as Schedule 3, but are exempt from the safe custody requirements (see new legal requirements and resources for prescribers and dispensers below)
- evaluate patients carefully for a history of drug abuse and dependence before prescribing pregabalin and gabapentin
- observe patients on pregabalin and gabapentin for possible signs of abuse and dependence, for example, drug-seeking behaviour, dose escalation, and development of tolerance
- ensure patients are aware of the risk of potentially fatal interactions with other medicines that cause CNS depression, particularly opioid medicines, and with alcohol
- report suspected adverse drug reactions to pregabalin and gabapentin on a [Yellow Card](#), including cases of abuse and dependence

### **Risk of abuse and dependence**

The product information for gabapentin and pregabalin contain warnings about cases of abuse and dependence. Patients should be carefully evaluated for a history of drug abuse and observed for possible signs of misuse, abuse, or dependence. These include, for example, drug-seeking behaviour, dose escalation, and development of tolerance.

As for all medicines, patients should be given information on the expected benefits and potential risks of pregabalin and gabapentin, including through provision of the Patient Information Leaflet at dispensing. Prescribers should be aware of all medicines (including any over-the-counter products or illicit drugs) patients are taking to minimise or avoid drug interactions.

### **Cases reported of abuse and dependence in the UK**

The MHRA monitors the benefits and risks of medicines in the UK and asks healthcare professionals and patients to report cases of abuse and dependence associated with medicines. Since authorisation and up to 10 April 2019, we have received 113 reports of abuse and 98 reports of dependence with pregabalin. Since authorisation and up to 10 April 2019, we have received 11 reports of abuse and 9 reports of dependence associated with gabapentin.

Gabapentin and pregabalin can cause depression of the central nervous system, resulting in drowsiness, sedation, and potentially fatal respiratory depression, particularly if used concomitantly with opioid medicines and alcohol.

### **New legal requirements for pregabalin and gabapentin**

As of 1 April 2019, pregabalin and gabapentin are classified as Class C controlled substances (under the Misuse of Drugs Act 1971) and scheduled under the Misuse of Drugs Regulations 2001 (as amended) as Schedule 3 for Great Britain. For legislation changes, see [S.I. 2018/1356](#) and [S.I. 2018/1383](#) of The Misuse of Drugs and Misuse of Drugs (Safe Custody) (Amendment) (England and Wales and Scotland) Regulations 2018. These legal changes are mirrored in legislation for Northern Ireland in [the Misuse of Drugs and Misuse of Drugs \(Safe Custody\) \(Amendment\) Regulations \(Northern Ireland\) 2019](#).

Following these changes, it is illegal for people to possess pregabalin and gabapentin without a prescription and illegal for a patient to supply or sell them to others (see NHS England [patient leaflet](#)).

### **Prescribers – responsibilities and resources**

Prescribers need to adhere to guidance for prescribing of medicines of this Class and Schedule (see [NHS England guidance document](#), and [advice for prescribers in Wales](#) from the Chief Pharmaceutical Officer)

Resources available for prescribers about the change (other resources may be available):

- NHS England [briefing note](#) for GP practices in England
- [Resources from the BNF on controlled drugs](#)
- [Pharmaceutical Services Negotiating Committee Controlled Drug prescription forms and validity](#)

### **Pharmacists – responsibilities and resources**

Prescriptions need to be dispensed by a pharmacist within 28 days of the prescription being written. Pregabalin and gabapentin are in the list of “exempted drugs” in the safe custody regulations for pharmacies. Pharmacies will need to denature before disposal.

Resources available for pharmacists about the change (other resources may be available):

- [Royal Pharmacological Society guidance for pharmacy](#)
- [Pharmaceutical Services Negotiating Committee guidance on dispensing controlled drugs](#)
- NHS England [briefing note](#) for pharmacies in England
- NHS England letter on the [handling of gabapentin and pregabalin in health and justice commissioned services](#)
- [Alert for dispensers in Wales from the Chief Pharmaceutical Officer](#)
- [Resources from the BNF on controlled drugs](#)

### **Government review of misuse**

In 2016, following concerns about misuse, illegal diversion, and dependence, the [Advisory Council on the Misuse of Drugs \(ACMD\)](#) recommended that both pregabalin and gabapentin, their salts and their esters are:

- controlled under the Misuse of Drugs Act 1971 as Class C substances
- scheduled under the Misuse of Drugs Regulations 2001 (as amended) as Schedule 3

The Home Office accepted the ACMD's advice but as a result of the public consultation, pregabalin and gabapentin are also being inserted into Schedule 1 to the Misuse of Drugs (Safe Custody) Regulations 1973, which means that they are exempted from the safe custody requirements under the 1973 Regulations.

As for all medicines, the MHRA will continue to closely monitor the benefits and risks of pregabalin and gabapentin and take action as required.

### **Background**

Gabapentin ([Neurontin](#)) is indicated as monotherapy or adjunctive therapy for partial seizures with and without secondary generalisation. It is also indicated for peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia (see [NHS website guidance for patients](#))

Pregabalin ([Lyrica](#)) is indicated as adjunctive therapy for partial seizures with or without secondary generalisation. It is also indicated for peripheral and central neuropathic pain and for generalised anxiety disorder (see [NHS website guidance for patients](#)).

### **Call for reporting**

Report suspected adverse drug reactions, including those associated with abuse or dependence, to the [Yellow Card Scheme](#). Your report helps the MHRA to monitor the safety of medicines and take action to prevent future harm.

*Article citation: Drug Safety Update volume 12, issue 9: April 2019: 4.*

## **Elvitegravir boosted with cobicistat: avoid use in pregnancy due to risk of treatment failure and maternal-to-child transmission of HIV-1**

Pharmacokinetic data indicate exposure of elvitegravir boosted with cobicistat (Genvoya ▼, Stribild) is lower during the second and third trimesters of pregnancy than postpartum. Low elvitegravir exposure may be associated with an increased risk of treatment failure and an increased risk of HIV-1 transmission to the unborn child, and therefore elvitegravir/cobicistat should not be used during pregnancy.

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

- pharmacokinetic data show low exposure values of elvitegravir boosted with cobicistat (elvitegravir/cobicistat) during the second and third trimesters of pregnancy
- although no cases have been reported of such transmission on therapy to date, low elvitegravir exposure may be associated with an increased risk of treatment failure and an increased risk of mother-to-child transmission of HIV infection
- therapy with elvitegravir/cobicistat should not be initiated during pregnancy
- switch women who are pregnant and taking elvitegravir/cobicistat to an alternative regimen
- report suspected adverse drug reactions with HIV medicines to the Yellow Card Scheme, including treatment failure that results in harm

### **Background**

Elvitegravir is an integrase inhibitor that is used as one of the concomitant antiretroviral therapies to treat HIV-1. Cobicistat is a pharmacokinetic enhancer used to increase elvitegravir levels.

Cobicistat is available on its own as a medicine called Tybost. Medicines in which elvitegravir/cobicistat are provided together are Genvoya ▼ (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide) and Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil).

### **Data for lower exposure in pregnancy**

In July 2018, we issued warnings not to use [darunavir boosted with cobicistat](#) in pregnancy after pharmacokinetic data suggested an increased risk of treatment failure and mother-to-child transmission of HIV infection due to lower exposures during pregnancy.

The risk in treatments containing elvitegravir/cobicistat has also been reviewed.

Pharmacokinetic data from [IMPAACT P1026s](#) (International Maternal Pediatric Adolescent AIDS Clinical Trials P1026 study) show that compared with paired postpartum data, plasma concentration after 24 hours of elvitegravir boosted with cobicistat was 81% lower in the second trimester and 89% lower in the third trimester. Plasma concentration after 24 hours of cobicistat was 60% and 76% lower in the second and third trimester, respectively.

A review of safety data and the published literature has not to date identified any cases of mother-to-child HIV-1 transmission in women taking regimens containing elvitegravir/cobicistat during the second and third trimesters of pregnancy. However, due to the theoretical risk, therapy with elvitegravir/cobicistat should not be initiated during pregnancy and women who are pregnant and taking elvitegravir/cobicistat should be switched to an alternative regimen.

### **Updates to product information**

The product information for [Genvoya ▼](#) (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide) and [Stribild](#) (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil) are being updated to recommend against use in pregnancy and a [letter has been sent to relevant healthcare professionals](#) to inform them of this information.

[Letter sent to healthcare professionals. March 2019.](#)

### **Report suspected adverse drug reactions with HIV medicines**

Report any suspected adverse drug reactions with black triangle drugs such as Genvoya ▼ on a [Yellow Card](#). Any cases of mother-to-child transmission of HIV due to lack of efficacy of medicines used in HIV should be reported on a [Yellow Card](#).

*Article citation: Drug Safety Update volume 11, issue 9; April 2019: 5.*

## Letters and drug alerts sent to healthcare professionals in March 2019

### Letters

- [Xeljanz ▼ \(tofacitinib\): Increased risk of pulmonary embolism and mortality in rheumatoid arthritis patients receiving 10 mg twice daily in a clinical trial](#)
- [Ranitidine 150 mg tablets: Batch number and expiry date prompts 'LOT' and 'EXP' printed in German on outer \(carton\) packaging](#)
- [Nulojix \(belatacept\): Update on the temporary restriction in supply \(initiated in March 2017\)](#)
- [Fluoroquinolone antibiotics: risk of disabling, long-lasting and potentially irreversible side effects](#) – New restrictions on prescribing for ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin for safety reasons
- [Genvoya ▼ \(elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide\), Stribild ▼ \(elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil\), Tybost \(cobicistat\): Increased risk of treatment failure and increased risk of mother-to-child transmission of HIV infection due to lower exposure of elvitegravir and cobicistat during the second and third trimesters of pregnancy](#)
- [Belimumab \(Benlysta ▼\): Increased risk of serious psychiatric events \(depression, suicidal ideation or behaviour, or self-injury\)](#)

[Class 2 Medicines recall of Accord Healthcare Losartan Potassium 50mg Film-coated Tablets, PL 20075/0022 and Losartan Potassium 100mg Film-coated Tablets, PL 20075/0023](#) due to contamination with N-nitroso-N-methylamino butyric acid (NMBA).

#### **Actions for healthcare professionals:**

- Stop supplying the [batches listed in the alert](#) immediately. Quarantine all remaining stock and return to your supplier using your supplier's approved process.
- If you receive queries about this issue from patients, advise them to continue 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 losartan potassium containing products. In case of local supply issues, patients should be advised to speak to their doctor to discuss alternative treatments.

The MHRA continues to thoroughly investigate nitrosamine contamination alongside the European Medicines Agency (EMA) and the European Directorate for the Quality of Medicines (EDQM). We will continue to monitor the situation in the UK and consider what actions are necessary to protect public health.

## Other drug alerts

In March 2019, a [company-led drug alert was issued for Ozurdex implants](#) (MDR 95-08/18) due to the possibility that a single loose silicone particle of approximately 300 microns in diameter may become detached – see also [letter to healthcare professionals](#) from February 2019.

For the latest alerts, including those from April 2019 on Nutriflex Omega Special 2500ml, chloramphenicol 0.5% W/V antibiotic eye drops, and zoledronic acid 5 mg solution for infusion, see [Alerts and recalls for drugs and medical devices](#).

*Article citation: Drug Safety Update volume 12, issue 9: April 2019: 6.*

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

[Pagewriter Cardiographs \(TC20/30/50/70\) manufactured before 20 November 2018 and Efficia Monitors \(CM10/12/100/120/150\) manufactured before 25 October 2018 – risk of batteries overheating or igniting \(MDA/2019/017\)](#). Issued 20 March 2019. Manufactured by Philips – this problem affects lithium ion batteries that have exceeded their specified replacement interval or number of charging cycles.

[Fresenius 5008 & 5008S haemodialysis machines – low risk of inadequate fluid removal during treatment \(MDA/2019/018\)](#). Issued 29 March 2019. Manufactured by Fresenius Medical – inadequate ultrafiltration can occur due to sudden failure of the ultrafiltration (UF) pump.

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