

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 15 Issue 9 April 2022

Contents

| | |
|--|--------|
| Pregabalin (Lyrica): findings of safety study on risks during pregnancy | page 2 |
| COVID-19 vaccines and medicines: updates for April 2022 | page 7 |
| Letters and medicine recalls sent to healthcare professionals in March 2022 | page 9 |

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.



NICE has accredited the process used by the MHRA to produce Drug Safety Update guidance. More information on accreditation can be viewed on the [NICE website](https://www.nice.org.uk/accreditation).

To subscribe to monthly email alerts of Drug Safety Update see: <https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency/email-signup>

First, we have advice to prescribers of pregabalin, which is used in neuropathic pain, generalised anxiety disorder, and as adjunct treatment for some types of seizures. A new study has suggested that pregabalin may slightly increase the risk of major congenital malformations if used in pregnancy. The observational study of more than 2,700 pregnancies exposed to pregabalin suggested use in the first trimester to be associated with a slightly increased risk of major congenital malformations compared with exposure to no antiepileptic drugs or to lamotrigine or to duloxetine. Patients should continue to use effective contraception during treatment and avoid use in pregnancy unless clearly necessary. We also provide advice for healthcare professionals to use with patients to aid discussions on what this might mean for them.

On page 7, we summarise recent advice relating to COVID-19 vaccines and medicines published since the March 2022 issue of Drug Safety Update. This includes recent approval of the Valneva COVID-19 Vaccine, approval of Evusheld (tixagevimab/cilgavimab) for COVID-19 prevention, and updates to the pregnancy and breastfeeding information for Spikevax COVID-19 Vaccine and Comirnaty COVID-19 Vaccine.

And on page 9, we include recent letters, recalls, and notifications sent to healthcare professionals about medicines and medical devices. This includes a recall of all Accuretic (quinapril hydrochloride and hydrochlorothiazide) tablets due to the observation of an impurity above the acceptable daily intake level.

Pregabalin (Lyrica): findings of safety study on risks during pregnancy

A new study has suggested pregabalin may slightly increase the risk of major congenital malformations if used in pregnancy. Patients should continue to use effective contraception during treatment and avoid use in pregnancy unless clearly necessary.

Advice for healthcare professionals:

- an observational study of more than 2,700 pregnancies exposed to pregabalin has shown use in the first trimester to be associated with a slightly increased risk of major congenital malformations compared with exposure to no antiepileptic drugs or to lamotrigine or to duloxetine – see details of the study data on page 4
- continue to provide counselling to patients using pregabalin on:
 - the potential risks to an unborn baby (see [separate patient safety leaflet](#))
 - the need to use effective contraception during treatment
- continue to avoid use of pregabalin during pregnancy unless clearly necessary and only if the benefit to the patient clearly outweighs the potential risk to the fetus – ensure the patient has a full understanding of the benefits, risks, and alternatives, and is part of the decision-making process
- advise patients planning a pregnancy or who become pregnant during treatment to make an appointment to discuss their health condition and any medicines they are taking
- in cases where the benefit outweighs the risk, and it is clearly necessary that pregabalin should be used during pregnancy, it is recommended to:
 - use the lowest effective dose
 - report any suspected adverse drug reactions, including for the baby, via the [Yellow Card scheme](#)

Reminder for prescribers of ANY antiepileptic drug:

- at initiation and as part of the recommended annual review for patients with epilepsy, discuss the risks associated with antiepileptic drugs and with untreated epilepsy during pregnancy and review their treatment according to clinical condition and circumstances – see [advice for antiepileptic drugs in pregnancy](#)
- urgently refer anyone planning a pregnancy or who is suspected to be pregnant for specialist advice on their antiepileptic treatment
- if a patient is planning to have a baby, offer 5mg per day of folic acid before any possibility of pregnancy

Pregabalin indications and scope of this advice

[Pregabalin](#) (brand names Alzain, Axalid, Lecaent, Lyrica, plus generic versions) is indicated for the treatment of peripheral and central neuropathic pain in adults, as adjunctive therapy in adults with partial seizures with or without secondary generalisation, and for generalised anxiety disorder in adults (see [NHS Guidance](#)).

The advice in this article is relevant for patients taking pregabalin who are pregnant or may become pregnant.

Previous reviews of pregabalin in pregnancy

Following a national review into the safety of antiepileptic drugs in pregnancy, including pregabalin, in January 2021 we published new safety advice in [Drug Safety Update](#) with [patient advice](#), and a [Public Assessment Report](#).

At the time of publication, we noted that due to conflicting data, no firm conclusions could be drawn on the potential teratogenic effect of pregabalin. This review included one US cohort study of 477 infants exposed to pregabalin in the first trimester, which did not show an increased risk after adjustment, but was unable to rule out a small effect on the rate of congenital malformations.¹ The review considered preliminary data from a study, from which further information and analyses have become available and evaluated (as below).

¹ [Patorno E and others](#).
Neurology 2017;
volume 88,
pages 2020 to
2025.

At the time, the product information noted that the potential risk for humans in pregnancy was unknown. As such, patients were advised to use effective contraception and avoid pregabalin in pregnancy unless necessary.

New review of study of pregabalin in pregnancy

Fuller data is now available from a Nordic observational study of more than 2,700 pregnancies exposed to pregabalin in the first trimester (see detailed description on page 4).

We have carefully reviewed the results of the study alongside a recent European review of the same findings. The review concluded that pregabalin use during the first trimester of pregnancy may cause a slightly increased risk of major congenital malformations in the unborn child.

The MHRA has considered the recommendations of the European review, together with the other limited safety data available regarding pregabalin safety in pregnancy, and agreed that the product information should be updated to include information from this study. The [Summary of Product Characteristics](#) and [Patient Information Leaflet](#) has now been updated.

The product information continues to advise that effective contraception should be used during treatment and that use in pregnancy avoided unless clearly necessary.

Healthcare professionals are advised to consider our [guidance on contraceptive methods](#), and take into account the patient's personal circumstances when advising on contraception.

Detailed information on study and outcomes data

Study design and population

The [Pregabalin pregnancy outcomes study](#) was a population-based cohort study.² The [study](#) used data from national administrative registries from 4 Nordic countries (Denmark, Finland, Norway, and Sweden) to characterise pregnancy outcomes.

² [Toft G. and others](#). Last accessed March 2022.

The study examined use of pregabalin in all authorised indications. The prevalence of usage for each indication of pregabalin differed between the countries, but (where recorded) it was most commonly prescribed for anxiety and neuropathic pain. This is thought to be similar to the clinical situation in the UK.

The exposure data from the study indicated that the proportion of women using pregabalin in pregnancy had increased over the 10-year period (up to 2015/2016) and that exposure to pregabalin in pregnancy was most frequent in the first trimester.

Prescribers of these medicines should continue to follow the current recommendations on patient monitoring.

Study methods and comparator groups

Following a national review into the safety of antiepileptic drugs in pregnancy, including pregabalin, in January 2021 we published new safety advice in [Drug Safety Update](#) with [patient advice](#), and a [Public Assessment Report](#).

At the time of publication, we noted that due to conflicting data, no firm conclusions could be drawn on the potential teratogenic effect of pregabalin. This review included one US cohort study of 477 infants exposed to pregabalin in the first trimester, which did not show an increased risk after adjustment, but was unable to rule out a small effect on the rate of congenital malformations.¹ The review considered preliminary data from a study, from which further information and analyses have become available and evaluated (as below).

At the time, the product information noted that the potential risk for humans in pregnancy was unknown. As such, patients were advised to use effective contraception and avoid pregabalin in pregnancy unless necessary.

Study findings for major congenital malformations

Full study findings are [published online](#).

The study showed a higher prevalence of major congenital malformations in the babies (live or stillborn) exposed to pregabalin in the first trimester of pregnancy (crude percentage 5.9%) compared with those not exposed to pregabalin or any other antiepileptic drug (crude percentage 4.1%). After adjustment, the risk of major congenital malformations was slightly higher but not statistically significant with pregabalin monotherapy use in the first trimester versus the comparison group (adjusted prevalence ratio 1.14 (95% confidence interval (95% CI) 0.96 to 1.35)).

The data suggested modest but statistically significantly increased risks (less than 2-times) of major congenital malformations in pregnancies exposed to pregabalin compared with pregnancies exposed to lamotrigine or duloxetine. The adjusted prevalence ratios for congenital malformations with first-trimester pregabalin monotherapy were 1.29 (95% CI 1.01 to 1.65) versus lamotrigine and 1.39 (1.07 to 1.82) versus duloxetine.

Slightly higher risks of specific malformations of the nervous system, eye, face (orofacial clefts), urinary system, and genitals were observed in babies exposed to pregabalin compared with those exposed to the other medicines or in the comparison population. However, estimates may be imprecise due to the low number of cases. Effects on the central nervous system and eye defects have also been observed in animals in preclinical studies.

Limitations in the study findings for major congenital malformations

This study was observational and based on registries. Comparisons of outcomes between the patients taking pregabalin and patients taking other medicines, or no antiepileptic drugs, may have been affected by other factors that affect the risk of congenital malformations (confounding).

Other factors include that the study did not take into account the purpose for which lamotrigine or duloxetine were being used, and so there might have been differences due to the underlying medical conditions.

That being said, although the risk estimates in the study are modest and some are not statistically significant, this is the largest population-based study currently available and there is an indication of a slight increased risk of major congenital malformations with use of pregabalin in the first trimester. It is important for patients to receive this information and consider it carefully with their prescriber.

It is noted that the prevalence of major congenital malformations in the comparison group (not exposed to any antiepileptic drug during the first trimester) was higher than the estimated prevalence in the UK general population (2–3%). This may be due to differences between the Nordic registries and UK studies in how they measure and categorise congenital malformations. It may also possibly reflect improved diagnoses of these conditions over the study period.

Study findings for other birth outcomes and postnatal neurodevelopmental outcomes

The study also examined the risk of other birth outcomes (stillbirth, small for gestational age, low birth weight, preterm birth, low Apgar score at 5 minutes, and microcephaly) and neurodevelopmental outcomes (attention deficit hyperactivity disorder, autism spectrum disorders and learning disabilities).

The small numbers of cases and limited follow-up time of exposed live-birth infants meant that firm conclusions on these other birth and neurodevelopmental outcomes cannot be drawn. These risks remain uncertain and we will continue to keep under close review.

Antiepileptic medicines in pregnancy: new registry

We remind all healthcare professionals of the actions required of them following the 2021 [antiepileptic medicines in pregnancy review](#).

The MHRA and NHS Digital are working together on the [Medicines in Pregnancy Registry](#), which is built around a core register of routinely collected prescribing data for all women in England who are taking NHS-prescribed valproate and other antiepileptic medications. Healthcare professionals can use the data provided to review comparative use of antiepileptic medicines in pregnancy. The [report from the registry](#) was updated on 31 March 2022 to include data up to September 2021. An [interactive dashboard](#) is available to review the data and how prescribing of antiepileptic medicines in pregnancy has changed over time.

Further resources for prescribers

Clinicians should continue to use resources for prescribers about medicines of potential teratogenic effects. The [UK Teratology Information Service](#) provides independent advice about the risks and benefits of medicines use in pregnancy.

Report suspected reactions on a Yellow Card

Please continue to report any suspected adverse drug reactions (ADRs) associated with pregabalin or any other medicines via the [Yellow Card scheme](#).

Please report any suspected ADRs associated with [medicines taken during pregnancy or breastfeeding](#), including any suspected effects on the baby or child. All patients, caregivers, and healthcare professionals can report a Yellow Card when they suspect a medication used during pregnancy has caused an adverse reaction or adverse pregnancy outcome.

When reporting ADRs related to medicines used in pregnancy, the following information is particularly valuable for our assessment of the report:

- Timings of when the medicine was taken during the pregnancy
- The outcome of the pregnancy (when known)
- Details of any relevant family history, including any obstetric history
- For reports concerning congenital malformations, a detailed clinical description of any congenital anomaly and the results of any imaging (for example, scans), or laboratory tests

Please include any other relevant information, including other medications or substances taken during the pregnancy, as well as folic acid intake.

Report Yellow Cards using:

- the [Yellow Card website](#)
- the Yellow Card app; download from the [Apple App Store](#) or [Google Play Store](#)
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

Report suspected side effects to medicines, vaccines or medical device and diagnostic adverse incidents used in coronavirus (COVID-19) using the [dedicated Coronavirus Yellow Card reporting site](#) or the Yellow Card app. See the MHRA website for the [latest information on medicines and vaccines for COVID-19](#).

Article citation: Drug Safety Update volume 15, issue 9: April 2022: 1.

COVID-19 vaccines and medicines: updates for April 2022

Recent information relating to COVID-19 vaccines and medicines that has been published since the March 2022 issue of Drug Safety Update, up to 14 April 2022.

Updates to the pregnancy and breastfeeding information for Spikevax COVID-19 vaccine and Comirnaty COVID-19 Vaccine

We have made changes to the product information for the Spikevax COVID-19 Vaccine and the Comirnaty COVID-19 Vaccine to reflect the large amount of real-world data on pregnancy and breastfeeding that has now been collected. The available data are reassuring on safety and that the vaccines can be used during pregnancy and breastfeeding – see recent [Yellow Card reporting for the COVID-19 vaccines](#).

A large amount of information from pregnant women vaccinated with Spikevax and Comirnaty during the second and third trimester has not shown negative effects on the pregnancy or the newborn baby.

Published studies from the USA and Norway have compared miscarriage rates for vaccinated and unvaccinated women who were pregnant over the same time periods. The studies included data from a large number of women (more than 15,000) who received the Spikevax or Comirnaty COVID-19 vaccines. Both studies found that the occurrence of miscarriage was equally likely amongst unvaccinated women as amongst women at the same stage of pregnancy who were vaccinated in the previous 3 to 5 weeks. These studies provide strong evidence for no increased risk of miscarriage in association with the mRNA vaccines in current use

The numbers of Yellow Card reports for pregnant women are low in relation to the number of pregnant women who have received COVID-19 vaccines to date. There is no pattern from the reports to suggest that any of the COVID-19 vaccines used in the UK, or any reactions to these vaccines, increase the risk of miscarriage, stillbirths, congenital anomalies or birth complications.

There is no current evidence that COVID-19 vaccination while breastfeeding causes any harm to breastfed children or affects the ability to breastfeed. Spikevax and Comirnaty can be given during breastfeeding.

For more information, see the Summary of Product Characteristics section 4.6 for [Spikevax](#) and [Comirnaty](#), and Patient Information Leaflet section 2 for [Spikevax](#) and [Comirnaty](#).

Approval of Valneva COVID-19 vaccine

We have approved the COVID-19 vaccine developed by Valneva after a rigorous review, and we found it met the required safety, quality and effectiveness standards.

For more information about the Valneva COVID-19 vaccine, please see our [Press release](#) and [Decision page](#), which includes the Summary of Product Characteristics and Patient Information Leaflet.

Approval of Evusheld (tixagevimab/cilgavimab) for COVID-19 prevention

We have authorised Evusheld (tixagevimab/cilgavimab), a new medicine for COVID-19 prevention after it met our regulatory standards of safety, quality and effectiveness.

For more information, please see our [Press Release](#) and [Decision page](#), which includes the [Summary of Product Characteristics](#) and [Patient Information Leaflet](#).

Summaries of Yellow Card reporting and other recent MHRA publications

We continue to publish the summaries of the [Yellow Card reporting for the COVID-19 vaccines](#) being used in the UK. The report summarises information received via the Yellow Card scheme and will be published regularly to include other safety investigations carried out by the MHRA under the [COVID-19 Vaccine Surveillance Strategy](#).

We have also recently:

- updated the [product information for Comirnaty 10 mg/dose concentrate](#) to reference the products orange cap and extended the shelf life from 6 months to 9 months. Also updated the [product information for Comirnaty 30 mg/dose concentrate](#) to reference the products purple cap, amended the frequencies for myocarditis and pericarditis from not known to very rare, added erythema multiforme as a potential side effect, updated the wording around the shelf life and included a reference to the new paediatric formulation for children aged 5 to 11 years.
- added paraesthesia as a rare side effect to the [product information of Spikevax COVID-19 Vaccine](#)
- published the [Public Assessment Report](#) for Xevudy (sotrovimab)
- approved an update to the current UK approval of the [Spikevax COVID-19 Vaccine that allows its use in Great Britain in 6 to 11 year-olds](#)

We previously included summaries of latest COVID-19 information, including in the [January 2022](#), [February 2022](#) and [March 2022](#) issues of Drug Safety Update. See [guidance on COVID-19 for all our latest information](#), including after publication of this article.

Reporting Yellow Cards

Report suspected side effects to medicines, vaccines, medical device and test kit incidents used in coronavirus (COVID-19) testing and treatment using the dedicated [Coronavirus Yellow Card reporting site](#) or via the Yellow Card app.

As these products are under additional monitoring, this includes all suspected adverse reactions associated with these vaccines. This will allow quick identification of new safety information. When reporting please provide as much information as possible, including information about medical history, any concomitant medications, onset, treatment dates, and vaccine product brand name and batch number.

You may be contacted following submission of a Yellow Card report so that we can gather additional relevant information for the assessment of the report. These contributions form an important part of our understanding of suspected adverse events.

Article citation: Drug Safety Update volume 15, issue 9: April 2022: 2.

Letters and medicine recalls sent to healthcare professionals in March 2022

Recall of Accuretic (quinapril hydrochloride and hydrochlorothiazide)

On 28 March 2022, all Accuretic (quinapril hydrochloride and hydrochlorothiazide) tablets were [recalled at pharmacy and wholesale level](#) as a precautionary measure due to the observation of levels of N-nitroso-quinapril (an impurity) above the acceptable daily intake level.

As a result of the recall, Accuretic will not be available to dispense from pharmacies. Currently no information can be provided for when Accuretic will be available again.

Based on the available data, there is no immediate risk to patients who have been taking this medication. Advise patients undergoing treatment not to discontinue Accuretic without consulting with their prescriber, as there are potential risks associated with suddenly stopping treatment for blood pressure.

See [accompanying letter](#) to provide advice to prescribers on impact on patient treatment. For patients who are already taking Accuretic, it will not be possible to continue treatment and the prescribing healthcare professionals should review their hypertension treatment and switch patients to a suitable alternative.

Other Letters

In March 2022, the following letters were sent or provided to relevant healthcare professionals:

- [Comirnaty ▼ 10 micrograms/dose concentrate for dispersion for injection \(tozinameran\): important shelf life update for COVID-19 mRNA Vaccine \(nucleoside-modified\) – children 5 to 11 years](#)
- [Spravato ▼ \(esketamine\) nasal spray: patients required to be enrolled in the Register And Alert System before administration to mitigate the risk of drug abuse](#)

Other Medicine Recalls and Notifications

In March 2022, recalls and notifications for medicines were issued on:

[Class 3 Medicines Recall: Kyowa Kirin Services Ltd. Isotard 60mg XL Tablets, EL \(22\)A/10](#). Issued 2 March 2022. A batch of Isotard XL (Isosorbide-5-mononitrate) tablets are being recalled due to the presence of microfibrils or crystals of the active ingredient present on the surface of the tablets. This is a precautionary recall and this issue has no impact on tablet efficacy, product or patient safety. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

[Class 2 Medicines Recall: Wockhardt UK Ltd, Diazepam RecTubes 2.5mg Rectal Solution, EL \(22\)A/11](#). Issued 7 March 2022. A batch of Diazepam RecTubes 2.5mg Rectal Solution is being recalled due to out of specification results during stability testing. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

[Class 4 Medicines Defect Information: Boots Company Plc, Decongestant Tablets and Decongestant with Pain Relief Tablets, EL \(22\)A/12](#). Issued 10 March 2022. Batches of Decongestant (Pseudoephedrine hydrochloride) tablets and Decongestant with Pain Relief Tablets (Paracetamol, Pseudoephedrine hydrochloride) have been identified that omits safety information from the Patient Information Leaflet. The omitted information includes contraindications in pregnancy and breastfeeding and side effects of ischaemic colitis and Ischaemic optic neuropathy. Healthcare professionals dispensing any of the affected batches are asked to provide the correct Patient Information Leaflet from the Electronic Medicines Compendium, to ensure that appropriate patient counselling takes place and patients are aware of the missing information.

[Class 4 Medicines Defect Information: CNX Therapeutics Ltd, Latuda film-coated tablets, EL \(22\)A/13](#). Issued 14 March 2022. The MHRA has been informed that batches of Latuda (lurasidone) 18.5mg, 37mg and 74mg film-coated tablets will be released without the EAN barcodes on the cartons. The expected distribution dates for these batches will take place between April 2022 and July 2022. Wholesalers and healthcare professionals should refer to the batch number and expiry date printed on the carton for stock control and dispensing.

[Class 4 Medicines Defect Information, Ayrton Saunders Limited, Beclometasone dipropionate 50 micrograms/dose Nasal Spray \(Various Liveries\), EL \(22\)A/14](#). Issued 15 March 2022. Batches of beclometasone dipropionate 50 micrograms / dose nasal spray in various liveries have been identified with incorrect braille, see the notification for full details. There is no issue with product quality and as these products are supplied as a single strength there are no possibilities of a dosing error occurring due to the error in the Braille. Healthcare professionals should explain the errors to patients who rely solely on Braille when reading medicine cartons.

[Company led medicines recall: Advanced Accelerator Applications NETSPOT \(Kit for the preparation of gallium Ga 68 dotatate injection\) \[unlicensed medicine\], CLMR \(22\)A/02](#). Issued 16 March 2022. Batches of NETSPOT (kit for the preparation of gallium Ga 68 dotatate injection) are being recalled by the company due to out-of-specification results obtained during stability studies. This is an unlicensed medicine and the manufacturer has full traceability. Stop supplying the batch immediately, quarantine all remaining stock and return to the company.

[Class 4 Medicines Defect Information: Benzylpenicillin benzathine 1.2 Million I.U. and 2.4 Million I.U. powder and solvent for suspension for injection, EL \(22\)A/15](#). Issued 17 March 2022. Batches of benzylpenicillin benzathine 1.2 Million and 2.4 million I.U. powder and solvent for suspension for injection have been identified with French labels on the 5mL ampoule of the water for injections solvent. The label on the vials, outer carton and Patient Information Leaflets are correct. Healthcare professionals are advised to note this issue.

Medical Device Safety Information

A recent MHRA National Patient Safety Alert has been published on:

[National Patient Safety Alert: Philips Health Systems V60, V60 Plus and V680 ventilators: potential unexpected shutdown leading to complete loss of ventilation \(NatPSA/2022/002/MHRA\)](#)

Issued 29 March 2022. Philips Health Systems have informed the MHRA of the risk of potential unexpected shutdowns of V60 and V60 Plus non-invasive ventilators, and V680 invasive ventilators used in critical care settings. The safety concern identified relates to a number of electrical faults in the devices, which can result in an unexpected shutdown, leading to loss of ventilation. If unnoticed by healthcare professionals, ventilation failure can have a severe health impact on patients. To manage this risk, the National Patient Safety Alert includes actions for all hospital trusts and other healthcare providers using the affected ventilators to be completed by 31 May 2022.

For all of the latest safety notices from the MHRA on drugs and medical devices, see [Alerts and recalls for drugs and medical devices](#).

Article citation: Drug Safety Update volume 15, issue 9: April 2022: 3.