Drug Safety Update

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

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Contents

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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First, we inform clinicians of the findings of a comprehensive safety review of antiepileptic drugs in pregnancy. We ask clinicians to use this information when discussing treatment options with women with epilepsy at initiation and at routine recommended annual review and with women who are planning to become pregnant.

Second, we include advice published on the COVID-19 vaccines authorised for use in the UK, including advice for people with allergies and for women during pregnancy and breastfeeding (see page 8).

Third, we inform clinicians that monitoring requirements and discontinuation criteria for dimethyl fumarate (Tecfidera) for multiple sclerosis have been strengthened following a small number of reports of progressive multifocal leukoencephalopathy (PML) in patients with mild lymphopenia. We also communicate new liver monitoring requirements and criteria for discontinuation for the multiple sclerosis medicine fingolimod, following cases of serious liver injury, including a few cases requiring transplantation (page 10).

On page 16, we inform of data from observational studies suggesting that the use of SSRI/SNRI antidepressants in the month before delivery may result in a small increased risk of postpartum haemorrhage.

On page 19, we advise on evidence suggesting an increased risk of ototoxicity associated with aminoglycoside antibiotics in patients with mitochondrial mutations. Genetic testing should not delay urgently needed aminoglycoside treatment but may be considered, especially before recurrent or long-term treatment.

Antiepileptic drugs in pregnancy: updated advice following comprehensive safety review

A review of the risks of major congenital malformations and of adverse neurodevelopmental outcomes for antiepileptic drugs by the Commission on Human Medicines has confirmed that lamotrigine (Lamictal) and levetiracetam (Keppra) are the safer of the medicines reviewed during pregnancy. This review was initiated in the context of the known harms of valproate in pregnancy, which should only be prescribed to women of childbearing potential **if there is a pregnancy prevention programme in place**.

Clinicians should use this information when discussing treatment options with women with epilepsy at initiation and at routine recommended annual reviews and in women planning to become pregnant.

Summary of key conclusions of review

- Lamotrigine – Studies involving more than 12,000 pregnancies exposed to lamotrigine monotherapy consistently show that lamotrigine at maintenance doses is not associated with an increased risk of major congenital malformations
- Levetiracetam – Studies involving more than 1,800 pregnancies exposed to levetiracetam do not suggest an increased risk of major congenital malformations
- For both lamotrigine and levetiracetam, the data on neurodevelopmental outcomes are more limited than those for congenital malformations. The available studies do not suggest an increased risk of neurodevelopmental disorders or delay associated with in-utero exposure to either lamotrigine or levetiracetam; however, the data is inadequate to rule out definitively the possibility of an increased risk
- For the other key antiepileptic drugs, data show:
    - an increased risk of major congenital malformations associated with carbamazepine, phenobarbital, phenytoin, and topiramate use during pregnancy
    - the possibility of adverse effects on neurodevelopment of children exposed in utero to phenobarbital and phenytoin
    - an increased risk of fetal growth restriction associated with phenobarbital, topiramate, and zonisamide use during pregnancy

Actions for prescribers

- At initiation and as part of the recommended annual review for patients with epilepsy, specialists should discuss with women the risks associated with antiepileptic drugs and with untreated epilepsy during pregnancy and review their treatment according to their clinical condition and circumstances – we have produced a safety information leaflet to assist with this discussion
- Urgently refer women who are planning to become pregnant for specialist advice on their antiepileptic treatment
- All women using antiepileptic drugs who are planning to become pregnant should be offered 5mg per day of folic acid before any possibility of pregnancy

- For lamotrigine, levetiracetam or any antiepileptic drugs that can be used during pregnancy, it is recommended to
  - use monotherapy whenever possible
  - use the lowest effective dose (see later for key dose monitoring advice, including for lamotrigine and levetiracetam)
  - report any suspected adverse effects experienced by the mother or baby to the Yellow Card scheme

Reminder of advice to give to women with epilepsy

- Do not stop taking antiepileptic drugs without discussing it with your doctor
- If you are taking an antiepileptic drug and think you may be pregnant, seek urgent medical advice, including urgent referral to your specialist
- Read the patient information leaflets that accompany your medicines and other information provided by your healthcare professional

Background

Antiepileptic drugs are crucial to control seizures and other epilepsy symptoms and untreated epilepsy can cause harm to both the mother and the unborn baby. However, use of these antiepileptic drugs during pregnancy has been associated with a range of harmful effects to the baby.

Valproate: reminder of the known risks and requirements

In particular, valproate (Epilim) is highly teratogenic and evidence supports a rate of congenital malformations of 10% in infants whose mothers took valproate during pregnancy and neurodevelopmental disorders in approximately 30% to 40% of children. For this reason, valproate should not be used in girls and women of childbearing potential unless other treatments are ineffective or not tolerated, as judged by an experienced specialist.

Valproate is contraindicated in women of childbearing potential unless a pregnancy prevention programme is in place. All healthcare professionals must continue to identify and review all female patients on valproate, including when it is used outside the licensed indications, and provide them with the patient information materials every time they attend their appointments or receive their medicines (including the patient information leaflet at dispensing).

The educational materials to support healthcare professionals and female patients on valproate were re-circulated to UK healthcare professionals by Sanofi in December 2020. We remind healthcare professionals that these materials must be used to ensure that the conditions of the valproate pregnancy prevention programme are met, as described in the documents.

National review of safety data

In the context of the known harms with valproate, the Commission on Human Medicines (CHM) has reviewed available safety data relating to the use of other key antiepileptic drugs in pregnancy for the risk of major congenital malformations, neurodevelopmental disorders and delay, and other effects on the baby. The key antiepileptic drugs were selected for the review on the basis of their place in UK clinical practice.

On this basis, data on the use of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, and zonisamide in pregnancy were reviewed. The data and conclusions from a European review in 2018 of levetiracetam in which the UK participated were also taken into account.

Full information on the antiepileptic drugs included in the review, in addition to studies considered and findings from these studies, can be found in the public assessment report. This report also includes a plain language summary of the review and findings.

How to use the review findings

We are communicating the conclusions of this review to help support decisions by prescribers and women who are starting or currently being treated with antiepileptic medicines. This information should also be considered when selecting a medicine for girls with epilepsy that may need treatment into adulthood and in particular for women planning a pregnancy.

At initiation and as part of the recommended annual review for patients with epilepsy, specialists should discuss with women the risks associated with antiepileptic drugs and with untreated epilepsy during pregnancy, and review their treatment according to their clinical condition and circumstances. We have produced a safety information leaflet to assist with this discussion. This advice for patients and their families and carers was developed following consultation with relevant stakeholder organisations, charities, and patient groups.

Where new information has been identified or where it is considered that product information (Summary of Product Characteristic (SmPC) and patient information leaflet) could be more informative, these will also be updated to reflect the latest information. For patient information leaflets for each medicine, we will be working with relevant patient groups to ensure that the information to patients is as clear as possible.

Some medicines included in the review are also authorised for medical conditions other than epilepsy (for example, pain and anxiety). Much of the evidence base relates to epilepsy and as such our review focused on the risks and decisions for epilepsy treatment. However, the advice in the product information should be considered to be relevant to any indication for these medicines where necessary.

Individual clinical decisions on the benefits and risks of using medicines during pregnancy may differ for other indications. As such, advice in this article and other materials (including the safety information leaflet) focuses on patients with epilepsy.

Key review findings

Major congenital malformations

Our review of risk of major congenital malformations assessed data from meta-analyses of epidemiological studies and other large epidemiological studies. The studies reviewed include comparisons of pregnancy outcomes between women given antiepileptic drug monotherapy and women without epilepsy or women with epilepsy who were not treated with antiepileptic drugs.

The results from these meta-analyses and other studies show that:

- a large amount of data exists for lamotrigine (more than 12,000 pregnancies exposed) and levetiracetam (more 1,800 pregnancies exposed) and these data do not suggest an increased risk of major congenital malformations when these antiepileptic drugs are used at the usual maintenance doses;
- for lamotrigine, studies investigating the effect of dose have shown conflicting results; one study using data from EURAP showed a statistically significant increase in the rate of major congenital malformations when doses of lamotrigine higher than 325mg per day were compared with doses of lamotrigine 325mg per day or lower. Other studies do not suggest dose-response effect on the risk of major congenital malformations.
- data for carbamazepine (around 9,000 pregnancies exposed), phenobarbital (around 1,800 pregnancies exposed), phenytoin (around 2,000 pregnancies exposed), and topiramate (around 1,000 pregnancies exposed) demonstrate that they are associated with an increased risk of major congenital malformations compared with that seen in the general population and women with epilepsy not on an antiepileptic drug
- the risk of major congenital malformations with carbamazepine, phenobarbital, and topiramate is dose-dependent
- the available data for pregabalin suggest it may be associated with a slightly increased risk of major congenital malformations, but these data include emerging findings that are currently under review and further evaluation is needed to reach definitive conclusions
- due to limitations of the data for gabapentin, oxcarbazepine, and zonisamide, the risk remains uncertain; the possibility of an increased risk of major congenital malformations can neither be confirmed nor ruled out

Neurodevelopmental disorders and delay

The review also considered meta-analyses and epidemiological studies that investigated the risk of adverse effects on neurodevelopmental outcomes including measures of intelligence, developmental outcomes, and symptoms or diagnoses of autism spectrum disorders in children exposed in-utero to antiepileptic drugs.

These data support the following conclusions:

- for carbamazepine, lamotrigine, and levetiracetam, data do not suggest an increased risk of neurodevelopmental disorders or delay, however, due to the limitations of these data the possibility of an increased risk cannot be definitively ruled out
- for phenobarbital and phenytoin, although the clinical studies report inconsistent findings, the totality of the data show the possibility of adverse effects on neurodevelopment
- some recent data raise concerns that topiramate use during pregnancy may be associated with poorer developmental outcomes, however, the numbers in the available studies remain limited and further data are needed to reach firm conclusions

- for gabapentin, oxcarbazepine, pregabalin, and zonisamide the data are either lacking, extremely limited or have limitations and the risks remain uncertain

Other effects during pregnancy

The available meta-analyses and epidemiological studies also provide data on the risk of fetal loss, prenatal growth restriction, and preterm birth associated with antiepileptic drug use during pregnancy.

These studies support that:

- use of lamotrigine or levetiracetam during pregnancy is not associated with an increased risk of fetal loss, prenatal growth restriction, or preterm birth;
- use of phenobarbital, topiramate, and zonisamide during pregnancy is associated with an increased risk of intrauterine growth retardation (small for gestational age)
- for carbamazepine, gabapentin, oxcarbazepine, and pregabalin, the risks associated with use during pregnancy remain uncertain

We will continue to review information for these risks as it becomes available. We encourage all healthcare professionals, patients, and caregivers to report any suspected effects associated with drugs taken during pregnancy, including on the neurodevelopment of a child, to the MHRA.

Monitoring and dosing advice in pregnancy

For any antiepileptic drug that is used during pregnancy, it is recommended to use monotherapy treatment and the lowest effective dose, where possible. Physiological changes during pregnancy (and post-partum) can affect concentrations of antiepileptic medicines, particularly for lamotrigine and phenytoin.

Key issues are described below. However, prescribers should consult advice from the SmPC and relevant clinical guidance for dosing and monitoring recommendations of any antiepileptic drugs in pregnancy.

Lamotrigine

There have been reports of decreased lamotrigine plasma levels during pregnancy with a potential risk of loss of seizure control. After birth, lamotrigine levels may increase rapidly with a risk of dose-related adverse events.

Therefore, lamotrigine serum concentrations in the woman should be monitored before, during, and after pregnancy, including shortly after birth. If necessary, the dose should be adapted to maintain the lamotrigine serum concentration at the same level as before pregnancy or adapted according to clinical response. In addition, dose-related undesirable effects should be monitored after birth.

Levetiracetam

Decrease in levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the third trimester (by up to 60% of baseline concentration before pregnancy). Appropriate clinical management of pregnant women treated with levetiracetam should be ensured.

Oxcarbazepine

Data from a limited number of women indicate that plasma levels of the active metabolite of oxcarbazepine, the 10-monohydroxy derivative (MHD), may gradually decrease throughout pregnancy. It is recommended that clinical response should be monitored carefully in women receiving oxcarbazepine during pregnancy to ensure that adequate seizure control is maintained. Measurement of MHD plasma concentrations should be considered. If dosages have been increased during pregnancy, postpartum MHD plasma levels may also be considered for monitoring.

Phenytoin

An increase in seizure frequency may occur during pregnancy because of altered phenytoin pharmacokinetics. Periodic measurement of plasma phenytoin concentrations may be valuable in the management of pregnant women as a guide to appropriate adjustment of dosage.

Report adverse drug reactions in pregnancy

Report any suspected adverse drug reactions in the mother or child following use of a medicine in pregnancy, including adverse pregnancy outcomes such as congenital malformations or adverse neurodevelopment outcomes, on a Yellow Card.

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
- For reports concerning adverse developmental outcomes, whether the child has met their key developmental milestones and whether they have had any further health issues

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

Report Yellow Cards electronically 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.

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COVID-19 vaccines (Pfizer/BioNTech and COVID-19 Vaccine AstraZeneca): current advice

Recent advice from the MHRA on the COVID-19 vaccines authorised for use in the UK, including advice for people with allergies and for women during pregnancy and breastfeeding.

The information in this article reflects understanding at the time of publication on 7 January 2021 and will not be actively updated with new information. See guidance on COVID-19 for all our latest information, including after publication of this article.

AstraZeneca COVID-19 vaccine approved

On 30 December 2020, the COVID-19 vaccine developed by Oxford University/AstraZeneca was given regulatory approval by the MHRA after meeting required safety, quality, and effectiveness standards. This followed a rigorous, detailed scientific review by the MHRA's expert scientists and clinicians and on the basis of the advice of its scientific, independent advisory body, the Commission on Human Medicines (CHM).

See Information for Healthcare Professionals, and Information for UK recipients about the COVID-19 Vaccine AstraZeneca. The vaccine has been approved for use for people 18 years or older and consists of a course of two doses, with the second dose administered 4–12 weeks after the first dose.

Further advice for the Pfizer/BioNTech vaccine

The COVID-19 vaccine developed by Pfizer/BioNTech was approved for use by MHRA on 2 December 2020.

The CHM has reviewed further data for the Pfizer/BioNTech vaccine as they have become available. On 30 December 2020, CHM recommended the following:

- **Allergies** – anyone with a previous history of allergic reactions to the ingredients of the vaccine should not receive it, but those with any other allergies such as a food allergy can now have the vaccine:
    - ingredients for the qualitative and quantitative composition of the Pfizer/BioNTech vaccine
    - ingredients for the excipient composition of the Pfizer/BioNTech vaccine
- **Pregnancy** – the vaccine should only be considered for use in pregnancy when the potential benefits outweigh any potential risks for the mother and baby. Women should discuss the benefits and risks of having the vaccine with their healthcare professional and reach a joint decision based on individual circumstances – see also the advice from Public Health England
- **Women who are breastfeeding** can be given the vaccine (this advice is in line with pregnancy and breastfeeding advice for the Oxford University/AstraZeneca vaccine)
- **Dosage interval** – the advice has been updated to say that the second dose of the Pfizer/BioNTech vaccine should be given at least 21 days after the first dose – see also the Letter from the UK Chief Medical Officers regarding the UK COVID-19 vaccination programmes

Updates have been made to Information for Healthcare Professionals and Information for UK recipients about the Pfizer/BioNTech vaccine to include these elements.

Reporting side effects

Healthcare professionals are asked to report any suspected side effects to COVID-19 vaccines. Report using the dedicated Coronavirus Yellow Card reporting site or the Yellow Card app.

Include the vaccine brand and batch/lot number in Yellow Card reports if available.

Reporting potential defects

In accordance with the published information and existing guidance, any potential defects identified by healthcare professionals should be managed as set out below.

1. Do not use the vial for vaccination.
2. Do not discard the vial, instead please keep it aside in a secure place as further investigation may be required.
3. Specifically, for the Pfizer/BioNTech COVID-19 vaccine, send any samples to "Pfizer Freepost 002", quoting PR# 5510321 on the front of the packaging.
4. Complete an MHRA Yellow Card (https://yellowcard.mhra.gov.uk/defective-products/) or contact the MHRA Defective Medicines Report Centre directly (DMRC@mhra.gov.uk).
5. In the usual way, report the issue to the National Vaccination Operations Centre (NVOC), via the agreed escalation process, including batch number and any other relevant details.

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Dimethyl fumarate (Tecfidera): updated advice on the risk of progressive multifocal leukoencephalopathy (PML) associated with mild lymphopenia

The monitoring requirements and discontinuation criteria for dimethyl fumarate (Tecfidera) have been strengthened following a small number of reports of progressive multifocal leukoencephalopathy (PML) in patients with mild lymphopenia. Continue to monitor lymphocyte counts and advise patients to seek urgent medical attention if they experience any symptoms or signs suggestive of PML

Advice for healthcare professionals:

- a small number of patients receiving dimethyl fumarate (Tecfidera) for the treatment of multiple sclerosis have developed PML associated with mild lymphopenia (defined as lymphocyte counts between 0.8x10⁹ per litre and the lower limit of normal [per local laboratory]); until now, other reported cases of PML were reported in patients with moderate to severe lymphopenia
- Tecfidera is contraindicated in patients with suspected or confirmed PML

Before starting treatment:

- do not start treatment in patients with severe lymphopenia (lymphocyte count of less than 0.5x10⁹ per litre)
- investigate patients with low lymphocyte counts for underlying causes of this before initiation

During treatment:

- all patients should have a lymphocyte count at least every 3 months
- conduct enhanced vigilance with close monitoring of lymphocyte counts and neurological symptoms in patients with lymphopenia and consider additional factors that may increase the risk of PML (see page 11)
- revaluate treatment in patients who have sustained moderate reductions of absolute lymphocyte counts (between 0.5x10⁹ per litre and 0.8x10⁹ per litre) for longer than 6 months
- stop treatment in patients who have prolonged severe lymphopenia for longer than 6 months
- Tecfidera must be permanently discontinued in any patient developing PML

Advice to give to patients:

- report suspected adverse drug reactions associated with fluoroquinolone antibiotics via the Yellow Card Scheme
- Tecfidera can lower the number of immune cells (lymphocytes) in the bloodstream and increase the risk of a viral infection in the brain (progressive multifocal leukoencephalopathy or PML); symptoms of PML can resemble those of a multiple sclerosis relapse
- be vigilant for any new or worsening neurological or psychiatric symptoms and seek urgent medical attention if they occur – these may include altered vision, weakness, confusion, speech problems, or personality changes lasting for more than a few days
- speak to your partner or carer about the risks and the need to seek medical attention if symptoms occur – they may notice symptoms that you are not aware of
- read carefully the patient information leaflet that comes with your medicine and keep it handy in case you need to read it again

Background

Dimethyl fumarate (Tecfidera) is authorised to treat adults with relapsing-remitting multiple sclerosis.

In clinical trials, lymphocyte counts decreased by approximately 30% from baseline values during Tecfidera treatment. We informed you of the risk of progressive multifocal leukoencephalopathy (PML) associated with prolonged moderate to severe lymphopenia caused by Tecfidera in March 2015 and April 2016.

PML is a rare serious opportunistic infection caused by the John-Cunningham virus (JCV), which may be fatal or result in severe disability. Risk factors for developing PML in the presence of JCV include an altered or weakened immune system.

Prescribers should be aware that mild lymphopenia during treatment with dimethyl fumarate is now considered a risk factor for PML and other factors may also increase the risk in the presence of lymphopenia.

Cases of PML with mild lymphopenia

A recent European review of safety data identified 11 cases of PML with lymphopenia associated with Tecfidera treatment, including 3 cases in patients with mild lymphopenia (lymphocyte counts defined as lymphocyte counts between 0.8x10⁹ per litre and the lower limit of normal [per local laboratory]). These reports were received within an estimated exposure to Tecfidera of more than 475,000 patients.[1]

1 Exposure data taken from letter to healthcare professionals. Sent Nov 2020

The risk of PML in patients with mild lymphopenia has been added to the product information (summary of product characteristics), alongside a new contraindication for suspected or confirmed PML. The marketing authorisation holder of Tecfidera has sent a letter to prescribers to inform of this new advice.

We have not received any UK reports via the Yellow Card scheme of confirmed PML cases associated with Tecfidera. However, we ask healthcare professionals to continue to be vigilant for suspected adverse drug reactions in UK patients and report any suspected cases (see Reporting instructions on page 12).

Patient monitoring advice

Lymphocyte counts should be checked before starting Tecfidera and continue to be monitored routinely every 3 months during treatment.

Lymphocyte counts and neurological symptoms should be monitored more closely in patients with lymphopenia. Prescribers should be aware that the following factors may further increase the risk of PML in individuals with lymphopenia:

- duration of treatment – PML has been diagnosed after approximately 1–5 years of Tecfidera treatment
- previous immunosuppressive or immunomodulatory treatment
- marked reductions in CD4+ and CD8+ T cell counts.

Magnetic resonance imaging (MRI) may be considered as part of increased vigilance for patients considered at increased risk of PML in accordance with local recommendations.

Physicians should continue to re-assess the balance of benefits and risks of Tecfidera treatment in patients with sustained moderate lymphopenia (defined as lymphocyte counts between $0.5x10^9$ per L and $0.8x10^9$ per L) for longer than 6 months.

Patients who have recently stopped natalizumab (Tysabri) may develop PML in the absence of lymphopenia.

Other medicines containing dimethyl fumarate

Dimethyl fumarate is also available as the medicine Skilarence, authorised to treat moderate to severe plaque psoriasis in adults. Prescribers of Skilarence should continue to follow the already stringent lymphocyte monitoring and discontinuation thresholds recommended for this medicine.

Reminder of actions required if PML is suspected

Healthcare professionals should continue to monitor patients on dimethyl fumarate for any signs of neurological dysfunction.

In any patient developing signs or symptoms suggestive of PML, dimethyl fumarate treatment should be stopped immediately and appropriate investigations conducted, including testing for John Cunningham virus (JCV) DNA in the cerebrospinal fluid using a quantitative polymerase chain reaction assay.

Report suspected reactions on a Yellow Card

Please continue to report suspected adverse drug reactions to the Yellow Card scheme.

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically 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)

When reporting please provide as much information as possible, including information about batch numbers, medical history, any concomitant medication, onset, treatment dates, and product brand name.

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.

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Fingolimod (Gilenya▼): updated advice about the risks of serious liver injury and herpes meningoencephalitis

Liver monitoring requirements and criteria for discontinuation of fingolimod have been updated following reports of serious liver injury. Fatal cases of encephalitis and meningitis caused by herpes simplex and varicella zoster viruses have also been reported during treatment. Advise patients to seek urgent medical attention if they develop any clinical features of liver dysfunction or meningoencephalitis. Discontinue fingolimod if significant hepatic injury or herpes meningoencephalitis is confirmed.

Advice for healthcare professionals:

- a small number of cases of clinically significant liver injury, including acute hepatic failure requiring transplantation, have been reported during fingolimod treatment
- monitor liver function tests (including bilirubin) routinely: before starting treatment; during treatment at months 1, 3, 6, 9 and 12; and then periodically until 2 months after discontinuation
- in patients without signs and symptoms of liver injury, the updated advice is:
    - monitor liver function tests more frequently if serum aspartate aminotransferase (AST) or serum alanine aminotransferase (ALT) levels exceed 3-times the upper limit of normal (ULN) but less than 5-times ULN with a normal bilirubin level
    - discontinue fingolimod if ALT or AST levels exceed 5-times ULN or if they are at least 3-times the ULN and bilirubin is increased – fingolimod may be re-started following a careful benefit-risk assessment of the underlying cause when serum levels have returned to normal
- in patients with symptoms or signs of hepatic dysfunction:
    - check liver function tests urgently
    - discontinue fingolimod if significant hepatic injury is confirmed; further treatment with fingolimod may be considered following recovery only if an alternative cause of hepatic dysfunction is established
- continue to be vigilant for infections with fingolimod; information has been updated to include herpes zoster/herpes simplex infections with visceral or CNS dissemination
- report any suspected adverse drug reactions to black triangle medicines such as fingolimod via the Yellow Card scheme

Advice to give to patients:

- fingolimod has been associated with a risk of serious liver injury and regular blood tests are needed to identify people at risk of liver damage before, during, and after treatment
- seek urgent medical attention if you develop any symptoms or signs of liver injury (such as feeling sick or vomiting (without another reason), tiredness, abdominal pain, jaundice (yellow skin or eyes), or dark urine
- serious and life-threatening cases of a type of brain infection (herpes meningoencephalitis) have been reported
- seek urgent medical attention if you experience any symptoms of a brain infection during fingolimod treatment and for 8 weeks after the last dose, including seizures (fits), headache, neck stiffness, oversensitivity to light, rash or fever
- read carefully the information booklet from your doctor and the patient information leaflet that accompanies your medicine and keep them handy in case you need to read them again

Risk of serious liver injury

Fingolimod (Gilenya) is authorised to treat patients aged 10 years or older with highly active relapsing-remitting multiple sclerosis that has not responded to at least one disease-modifying therapy or which is severe and rapidly progressive.

In clinical trials, 8% of adult patients receiving fingolimod 0.5mg daily developed increased ALT levels that exceeded 3-times the upper limit of normal (ULN) compared with 2% receiving placebo. Fingolimod was discontinued if serum transaminases were greater than 5-times ULN. Increased transaminase levels usually occurred within the first year of treatment and returned to normal within 2 months after discontinuation of fingolimod. Re-treatment resulted in increased transaminase levels in some patients, supporting a causal relationship.

A recent European review of safety data identified 7 cases of clinically significant liver injury that developed between 10 days and 5 years after the start of fingolimod treatment, including 3 post-marketing reports of acute hepatic failure requiring liver transplantation. Liver samples showed submassive hepatic necrosis in 2 patients, and one of these samples also contained features of acute hepatitis.

As of 31 August 2020, worldwide, more than 307,200 people (836,200 patient-years) with multiple sclerosis have been treated with Gilenya in clinical trials and routine clinical practice.[1] In the UK, just under 10,000 patients have received fingolimod (Gilenya) since it was marketed in 2011.[1]

1 Data provided by the Marketing Authorisation Holder.

We have not received any UK reports via the Yellow Card scheme of acute hepatic failure or serious liver injury (defined as AST or ALT at 3-times ULN or higher with increased bilirubin or jaundice) considered causally related to fingolimod treatment. However, we ask healthcare professionals to continue to be vigilant for suspected adverse drug reactions in UK patients and report any suspected cases (see Reporting instructions on page 15).

Due to the severity of recently reported cases, recommendations for liver monitoring and the discontinuation criteria have been strengthened to minimise the risks of liver injury. The marketing authorisation holder of Gilenya has sent a letter to prescribers to inform of this new advice.

New information on risk of meningoencephalitis

Advice in the product information regarding the risks of herpes zoster/herpes simplex infections with fingolimod has also been updated following the review's consideration of reported cases of infections with visceral or CNS dissemination, some of which were fatal.

Remind patients to seek immediate medical attention if they have a fever or signs of infection (including influenza or shingles) or if they have symptoms of meningitis or encephalitis during fingolimod treatment and up to 2 months after the last dose. See Drug Safety Update December 2017.

Resources available to support safe use

The product information and the educational materials will be revised to include updated advice for healthcare professionals and patients on the risks of serious liver injury and of herpes meningoencephalitis and cryptococcal meningitis.

Report suspected reactions on a Yellow Card

Please continue to report suspected adverse drug reactions (ADRs) to the Yellow Card Scheme. Fingolimod is a black triangle medicine and as such all ADRs should be reported.

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically 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)

When reporting please provide as much information as possible, including information about batch numbers, medical history, any concomitant medication, onset, treatment dates, and product brand name.

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.

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SSRI/SNRI antidepressant medicines: small increased risk of postpartum haemorrhage when used in the month before delivery

SSRIs and SNRIs are known to increase bleeding risks due to their effect on platelet function. Data from observational studies suggest that the use of SSRI/SNRI antidepressants during the month before delivery may result in a small increased risk of postpartum haemorrhage.

Prescribers should consider this risk in the context of an individual patient's bleeding and thrombotic risk assessment during the peripartum period and the benefits of antidepressants for the patient's mental health during this time.

Advice for healthcare professionals:

- SSRIs and SNRIs are known to increase the bleeding risk; observational data suggest that the use of some antidepressants in the last month before delivery may increase the risk of postpartum haemorrhage
- continue to consider the benefits and risks for use of antidepressants during pregnancy, and the risks of untreated depression in pregnancy
- healthcare professionals, including midwives, should continue to enquire about the use of antidepressant medicines, particularly in women in the later stages of pregnancy
- consider the findings of the review in the context of individual patient risk factors for bleeding or thrombotic events
- do not stop anticoagulant medication in women at high risk of thrombotic events in reaction to these data but be aware of the risk identified
- report any suspected adverse reactions associated with medicines taken during pregnancy via the Yellow Card Scheme

Review of bleeding risks

Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are two classes of commonly used antidepressant medicines. These medicines have been known for some time to increase the general risk of bleeding. This is thought to be due to serotonergic effect impairing platelet aggregation. Bleeding abnormalities associated with use of these medicines have been reported rarely and the absolute risk is thought to be low.

A recent EU review[1] considered spontaneous data in the context of a wider literature review for SSRI and SNRI medicines.[2,3,4] The review identified observational studies reporting an increased risk of postpartum haemorrhage in association with antidepressant use in late pregnancy, particularly for SSRIs and SNRIs.

Despite heterogeneous data and differences in definitions of postpartum haemorrhage, the review concluded that the data suggested a slightly increased risk of postpartum bleeding with use of SSRIs and SNRIs during the month before delivery. The review concluded that this risk might also apply to the newest antidepressant vortioxetine.

Following the review, warnings are being added to the product information for these medicines (list of products on page 17) to advise that they may increase the risk of postpartum haemorrhage.

1 European Medicines Agency. PRAC signal report October 2020.

2 Palmsten K and others. BMJ 2013; 347: f4877.

3 Bruning AH and others. Eur J Obstet Gynecol Reprod Biol 2015; 189: 38–47.

4 Jiang HY and others. J Psychiatr Res 2016; 83: 160-167.

Information about risks

Rates of postpartum haemorrhage vary by geographical region with one study suggesting rates in Europe of 12.7% with a blood loss greater than 500 millilitres and 2.8% with a blood loss greater than 1000 millilitres.[5]

5. Calvert C and others. PLoS ONE 2012; 7: e41114.

The review estimated that the use of antidepressant medicines in the month before delivery increases the risk by less than 2-fold. The severity of cases was not reported, but no fatalities were flagged in the dataset reported by the European review. Some datasets in the meta-analyses considered in the review defined all postpartum haemorrhage as blood loss of 500 millilitres or higher; some as 1000 millilitres.

Although the added risk of postpartum haemorrhage related to use of SSRI/SNRI antidepressants is small, it may be significant in individual patients when combined with other risk factors for post-partum haemorrhage. Updates to the patient information leaflets will include the increased risk, especially for patients with bleeding disorders. The leaflets will advise that the midwife or doctor should be made aware they are taking these medicines.

In the UK we have received a very small number of suspected adverse drug reactions (ADRs) reporting postpartum haemorrhage in association with antidepressant medicines. We ask clinicians to continue to be vigilant for ADRs associated with any medicines used during pregnancy and report them via the Yellow Card scheme (see page 18).

Assessment of thrombotic and bleeding risks for the peripartum period

The Commission on Human Medicines' Medicines in Women's Health Expert Advisory Group (MWHEAG) has considered the review findings and advised on the need to make healthcare professionals aware of the potential increased risk of bleeding in women who take SSRI/SNRI antidepressants in the month before delivery. They advised that these risks should be incorporated into the standard clinical risk assessment for bleeding and thrombotic risk.

MWHEAG advised that prescribers should encourage compliance with heparin self-administration in all patients with risk factors for venous thromboembolism (clinical guideline from RCOG). Clinical experience suggests approximately one-third of patients require heparin in the postpartum period after caesarean section to reduce the risk of venous thromboembolic events.

The benefits and risk of all medicines should be carefully considered, and the new data carefully communicated in the context of the risk of thromboembolic events.

Thromboembolic events in the peripartum period can have potentially fatal consequences. Women who have been prescribed heparin should be encouraged to adhere closely to the recommended dose and frequency of administration of heparin as advised by their doctor even if they are also taking SSRI or SNRIs.

Medicines affected

Taking the evidence into account, the review[1] considered there to be sufficient evidence to update the product information for:

- SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
- SNRIs: desvenlafaxine, milnacipran, venlafaxine
- Vortioxetine

Reminder of advice for use of antidepressants in pregnancy

Mental health conditions such as depression, particularly severe depression, can have serious consequences for both maternal and neonatal health. Healthcare professionals should continue to consider the benefits and risks for use of antidepressants during pregnancy, and the risks of untreated depression during pregnancy.

Use of SSRIs and SNRIs is associated with a risk of persistent pulmonary hypertension in the newborn and neonatal withdrawal and toxicity reactions. In 2010, we encouraged healthcare professionals to enquire about the use of SSRIs and SNRIs during pregnancy, particularly in women in the later stages of pregnancy.

Close observation of neonates exposed to SSRIs or SNRIs for signs of persistent pulmonary hypertension and withdrawal or toxicity effects is recommended after birth. The risks to newborn babies of exposure to SSRIs and SNRIs during pregnancy must be balanced with the risk to the mother and baby of untreated depression during pregnancy.

Report on a Yellow Card

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

Reporting for medicines in pregnancy

Please report any suspected ADRs associated medicines taken during pregnancy or breastfeeding experienced by the woman and any suspected effects on the baby or child.

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

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

Reporting for medicines in pregnancy

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically 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)

When reporting please provide as much information as possible, including information about batch numbers, medical history, any concomitant medication, onset, treatment dates, and product brand name.

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 14, issue 6: January 2021: 5.

Aminoglycosides (gentamicin, amikacin, tobramycin, and neomycin): increased risk of deafness in patients with mitochondrial mutations

Evidence suggests an increased risk of aminoglycoside-associated ototoxicity in patients with mitochondrial mutations, including cases in which the patient's aminoglycoside serum levels were within the recommended range. These mitochondrial mutations are rare and penetrance is uncertain. Genetic testing should not delay urgently needed aminoglycoside treatment but may be considered, especially before the start of recurrent or long-term treatment.

Advice for healthcare professionals:

- aminoglycoside use can result in rare cases of ototoxicity; some evidence suggests an association between mitochondrial mutations (particularly the m.1555A>G mutation) with an increased risk of this ototoxicity
- some cases reported ototoxicity in patients with mitochondrial mutations who had aminoglycoside serum levels within the recommended ranges
- these mitochondrial mutations are rare, and the penetrance of the observed increased ototoxic effect is unknown
- consider the need for genetic testing especially in patients, particularly in those requiring recurrent or long-term treatment with aminoglycosides, but do not delay urgent treatment in order to test
- when making prescribing decisions in patients with susceptible mutations, consider the need for aminoglycoside treatment versus alternative options available
- to minimise the risks of adverse events, including ototoxicity, continuous monitoring (before, during and after treatment) of renal function (serum creatinine, creatinine clearance) and auditory function, as well as hepatic and laboratory parameters, is recommended for all patients
- patients with known mitochondrial mutations or a family history of ototoxicity are advised to inform their doctor or pharmacist before they take an aminoglycoside
- report suspected adverse reactions experienced to the Yellow Card Scheme

Reminder of the risk of ototoxicity with aminoglycosides

Aminoglycosides are broad-spectrum bactericidal antibiotics. The group includes gentamicin, amikacin, tobramycin, and neomycin.

There is a narrow therapeutic window for aminoglycosides and their use can result in toxicity, including nephrotoxicity and ototoxicity, which can result in permanent hearing loss. This effect is related to the dose and duration of treatment and is exacerbated by renal or hepatic impairment or both and is more likely in elderly people and newborn babies.

To minimise the risk of ototoxicity with systemic aminoglycosides, regular serum concentration monitoring is recommended to maintain aminoglycoside levels below the toxic threshold for the cochleo-vestibular system. The product information for each medicine provides dosing considerations and recommendations for toxicity thresholds.

Assessment of auditory, vestibular, and renal function is particularly necessary in patients with additional risk factors.

Review of mitochondrial mutations and aminoglycoside ototoxicity

In 2020, we conducted a safety review following concerns received about the impact of mitochondrial mutations on the risk of ototoxicity with aminoglycosides. We identified several published epidemiological studies showing an increased risk of deafness in patients with the m.1555A>G mutation who were given aminoglycosides. There have also been reported cases of deafness in m.1555A>G patients with aminoglycoside use within the recommended serum levels. Some cases were associated with a maternal history of deafness or mitochondrial mutations or both.

Although no cases were identified with neomycin or topical preparations of gentamicin, amikacin, or tobramycin, based on a shared mechanism of action there is the potential for a similar effect with neomycin and other aminoglycosides that are administered at the site of toxicity (the ear).

The m.1555A>G mutation is the most common mitochondrial DNA (mtDNA) mutation, with an estimated prevalence of 0.2% in the general population.[1] The mutation is associated with sensorineural deafness and occurs in families with maternally transmitted deafness. Clinicians should follow local guidelines on mitochondrial mutation screening in patients with a maternal history of deafness or mitochondrial mutations or both and who require aminoglycoside therapy. Genetic screening may be especially appropriate in patients requiring recurrent or long-term aminoglycoside therapy where the risk of ototoxicity is increased.

Evidence and case reports

Our review focused on four key epidemiological studies[1,2,3,4] that reported an association between having mitochondrial mutations and an increased risk of deafness with aminoglycoside use. In addition, 10 case reports were identified from the medical literature indicating this toxicity. This evidence is further supported by a plausible biological mechanism where mutated mitochondrial ribosome more closely resembles the bacterial ribosome and may provide a binding site for aminoglycosides; this effect has been shown in biochemical tests.[5]

While many of the epidemiological studies had weak statistical power due to the rarity of the mitochondrial mutations, the evidence is considered sufficient to update the product information for aminoglycoside products with systemic absorption or that are administered at the site of toxicity (the ear).

The product information will be updated to include warnings of a potentially increased risk of ototoxicity in patients with known mitochondrial mutations. The patient information leaflet will ask patients to talk to their doctor or pharmacist before taking this medicine if they know (or think they have) a mitochondrial disease.

These mitochondrial mutations are rare, and the penetrance of the observed increased ototoxic effect is unknown. For patients known to have susceptible mutations, it is important to consider the need for aminoglycoside treatment and the alternative treatment options available when making prescribing decisions.

1 Göpel W and others. BMC Peds 2014; 14: 210.

2 Ealy M and others. Laryn 2011; 121: 1184-86.

3 Estivill X and others. AJHG 1998; 62: 27-35.

4 Johnson RF and others. Otalaryngol Head Neck Surg 2010; 142: 704-07.

5 Gao Z and others. J Otology 2017; 12: 1-8.

Report any suspected adverse drug reactions on a Yellow Card

Any suspected adverse drug reactions to aminoglycosides should be reported to us on a Yellow Card.

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically 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)

When reporting please provide as much information as possible, including information about batch numbers, medical history, any concomitant medication, onset, treatment dates, and product brand name.

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 14, issue 6: January 2021: 6.

Letters and drug alerts sent to healthcare professionals in December 2020

Letters

In December 2020, the following letters were sent or provided to relevant healthcare professionals:

- Systemic and inhaled fluoroquinolones: risk of heart valve regurgitation/incompetence
- Zerbaxa (ceftolozane / tazobactam) 1g/0.5g powder for concentrate for solution for infusion: global recall of product
- Epclusa▼ 200 mg/50 mg film-coated tablets (sofosbuvir/velpatasvir): supply of Irish product
- Lorazepam (Ativan 4mg/ml): temporary supply of a different presentation and changes to the instructions
- Briviact (Brivaracetam 10mg/ml) Oral Solution: Bottles with narrow neck diameter
- HyQvia▼ (human normal immunoglobulin and recombinant human hyaluronidase): crimping defect in hyaluronidase vial

Drug alerts

Class 3 Medicines Recall: Lupin Healthcare (UK) Limited, Simvador 10mg, 20mg and 40mg Tablets, EL (20)A/57. Issued 3 December 2020. Specific batches of simvastatin tablets are being recalled as these have been packaged with a version of the patient information leaflet (PIL) that does not include most up to date safety information. Although there is no risk to product quality, these affected batches are being recalled due to concerns around the omission of the safety information. All remaining stock should be quarantined and returned.

Class 4 Medicines Defect Information: Generics [UK] Limited t/a Mylan, EL(20)A/58. Issued 14 December 2020. Specific batches of perindopril erbumine medicines have been packaged with a version of the patient information leaflet (PIL) that does not include the most up to date safety information. If dispensing, make patients aware of missing information from the PIL provided in their packs.

Class 4 Medicines Defect Information, Co-Careldopa 25mg/100mg tablets, (PL 20242/0028), EL (20)A/59. Issued 15 December 2020. Specific batches contain cartons where the end-flap incorrectly states the active ingredient as ‘carbiopa’ instead of ‘carbidopa’. Healthcare professionals are advised to exercise caution when dispensing the product.

Class 2 Medicines Recall: Merck Sharp & Dohme Limited, Zerbaxa 1g/0.5g Powder for Concentrate for Solution for Infusion, EL (20)A/60. Issued 16 December 2020. Batches of this Zerbaxa (ceftolozane sulfate / tazobactam sodium) are being recalled as a precautionary measure due to retained batches showing presence of Ralstonia pickettii. Stop supplying the batch immediately and return to supplier. Patients are advised to speak to their doctor or pharmacist if they experience any worsening of symptoms or other side-effects.

Company led drug alert: Sodium chloride 0.9% Solution for injection (PL 08828/0178), EL (20)A/04. Issued 18 December 2020. A specific batch of sodium chloride is being recalled due to Polish-labelled ampoules within some of the cartons. Although there is no risk to product quality, as a precautionary measure packs with the listed batch number should be returned.

Class 2 Medicines Recall, medac GmbH (T/A medac Pharma LLP) Sodiofolin 50mg/ml Solution for Injection 100mg/2ml, PL 11587/0005, EL (20) A/61. Issued 29 December 2020. Specific batches of Sodiofolin are being recalled due to some inspected vials showing hairline damage to the shoulder of the vials. This is a second alert for further batches identified.

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