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 make healthcare professionals aware of a small increased risk of heart valve regurgitation (incompetence) associated with systemic and inhaled fluoroquinolone antibiotics. Prescribers should consider carefully other therapeutic options in patients at increased risk of heart valve regurgitation.

Next, we communicate advice for the antibiotic erythromycin. On page 5, we inform clinicians that erythromycin has been associated with cardiac events secondary to QT interval prolongation and should not be given to patients with a history of QT interval prolongation or ventricular cardiac arrhythmia, including torsades de pointes, or patients with electrolyte disturbances. On page 7, we inform of updates to the magnitude of the known risk of infantile hypertrophic pyloric stenosis following exposure to erythromycin, especially during the first 2 weeks of life.

We have approved a COVID-19 vaccine for supply in the UK. All vaccines are monitored by us, after approval.

Report any suspected side effect on the MHRA Coronavirus Yellow Card site https://coronavirus-yellowcard.mhra.gov.uk/.

Please see our website for updated information for healthcare professionals and the public.

Systemic and inhaled fluoroquinolones: small risk of heart valve regurgitation; consider other therapeutic options first in patients at risk

Fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients at risk for heart valve regurgitation (incompetence).

Advice for healthcare professionals:

- fluoroquinolones are authorised for use in serious, life-threatening bacterial infections
- systemic (by mouth or injection) and inhaled fluoroquinolones have been associated with a small increased risk of heart valve regurgitation, with one retrospective case-control study suggesting a 2-fold increased relative risk with current oral fluroquinolone use compared with the risk with use of amoxicillin or azithromycin
- fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in the following patients at risk:
    - patients with congenital heart valve disease or pre-existing heart valve disease
    - patients diagnosed with connective tissue disorders (for example, Marfan syndrome or Ehlers-Danlos syndrome)
    - patients with other risk factors or conditions predisposing for heart valve regurgitation (for example, hypertension, Turner's syndrome, Behçet's disease, rheumatoid arthritis, and infective endocarditis)
- advise patients, especially those at risk, of the importance of seeking immediate medical attention if they experience:
    - a rapid onset of shortness of breath, especially when lying down flat in bed
    - swelling of the ankles, feet, or abdomen
    - new-onset heart palpitations
- due to the small increased risk of aortic aneurysm and dissection, we have previously advised that fluoroquinolones should only be used after careful assessment of the benefits and risks in patients at risk of aneurysms and after consideration of other therapeutic options
- fluoroquinolones have also been associated with disabling, long-lasting or potentially irreversible adverse reactions affecting musculoskeletal and nervous systems – treatment should be discontinued at the first signs of a serious adverse reaction, including tendon pain or inflammation
- report suspected adverse drug reactions associated with fluoroquinolone antibiotics via the Yellow Card Scheme

Fluoroquinolones: previous prescribing advice

Fluoroquinolones are antibiotics approved for serious, life-threatening bacterial infections. UK authorised medicines include ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin. As for all antibiotic medicines, consideration should be given to official guidance on the appropriate use of antibacterial agents.

Fluoroquinolones have previously been associated with a small increased risk of aortic aneurysm and dissection. We have previously advised that fluoroquinolones should only be used after careful assessment of the benefits and risks in patients at risk of these events and after consideration of other therapeutic options. Patients at risk include those with a family history or previous history of aneurysm disease or those with other risk factors or conditions predisposing for aortic aneurysm and dissection (including some conditions listed in the Advice section above).

Fluoroquinolones have also previously been associated with an increased risk of disabling and potentially long-lasting, irreversible side effects affecting the musculoskeletal and nervous system, most commonly tendonitis and tendon rupture.

Tendon damage (especially to the Achilles tendon) can occur within 48 hours of starting fluoroquinolone treatment, but onset of symptoms and signs of the adverse reactions may be delayed several months after stopping treatment.

Following the review of these side effects, in 2019 the indications for all fluoroquinolones were restricted and new safety warnings introduced. These medicines should not be used for non-severe or self-limiting infections, non-bacterial conditions, or some mild to moderate infections unless other antibiotics that are commonly recommended are considered inappropriate.

The Drug Safety Update from March 2019 provides further detail on the important prescribing recommendations.

New data suggesting increased risk of heart valve regurgitation

A European review has considered data from epidemiological and non-clinical studies indicating an increased risk of heart valve regurgitation after use of fluoroquinolones.

An epidemiological study suggested an increased risk of aortic and mitral regurgitation associated with fluoroquinolone usage.[1] The case-control study of US patient records retrospectively examined a cohort of 12,502 patients with valvular regurgitation (after excluding patients with other conditions that may be associated with valvulopathy). Prescriptions of oral fluoroquinolones were compared with those of amoxycillin within this group and within a control cohort of 125,020 people.

1 Etminan M and others. *J Am Coll Cardiol* 2019; 74, 1444–50.

Patients with mitral or aortic regurgitation were nearly twice as likely to have been exposed to fluoroquinolones (2.4% of cases) than to amoxycillin (1.6% of cases). The study reported an adjusted rate ratio for current fluoroquinolones use versus amoxicillin use of 2.40 (95% CI 1.82 to 3.16) and versus current azithromycin use of 1.75 (95% CI 1.34 to 2.29).

A non-clinical study also reported that ciprofloxacin increases collagen degradation in heart muscle cells.

These findings indicate that systemic or inhaled fluoroquinolones might contribute to heart valve regurgitation, particularly in patients with pre-existing risk factors.
The increased risk of heart valve regurgitation has been added to the product information for these medicines and a letter sent to relevant healthcare professionals in the UK.

About heart valve regurgitation

Heart valve regurgitation, also called heart valve incompetence or insufficiency or leaking valve, occurs when blood flows back through the valves as they are closing or when they should be completely closed.

The risk of heart valve regurgitation is increased in the presence of risk factors such as pre-existing congenital heart valve disease or other risk factors or conditions predisposing for heart valve regurgitation, including connective tissue disorders (for example, Marfan syndrome, Ehlers-Danlos syndrome), hypertension, Turner's syndrome, Behcet's disease, rheumatoid arthritis, and infective endocarditis.

Some people with heart valve regurgitation may experience symptoms of heart failure, including:

- shortness of breath, especially when lying down flat in bed
- swelling of the ankles, feet, or abdomen
- new-onset heart palpitations

When initiating systemic or inhaled fluoroquinolone medicines, tell patients of the need to seek immediate medical attention if they develop the above signs and symptoms since they may suggest the presence of heart valve regurgitation.

Report suspected reactions on a Yellow Card

Please continue to report suspected adverse drug reactions 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 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 medical history, any concomitant medication, onset, treatment dates, and product brand name.

Article citation: Drug Safety Update volume 14, issue 5: December 2020: 1.

Erythromycin: caution required due to cardiac risks (QT interval prolongation); drug interaction with rivaroxaban

Erythromycin has been associated with events secondary to QT interval prolongation such as cardiac arrest and ventricular fibrillation. Erythromycin should not be given to patients with a history of QT interval prolongation or ventricular cardiac arrhythmia, including torsades de pointes, or patients with electrolyte disturbances.

A potential drug interaction between rivaroxaban and erythromycin resulting in increased risk of bleeding has also been identified.

Advice for healthcare professionals:

- be aware of reports of cardiotoxicity (QT interval prolongation) with macrolide antibiotics, in particular with erythromycin and clarithromycin
- erythromycin should not be given to:
  - patients with a history of QT interval prolongation (congenital or documented acquired QT interval prolongation) or ventricular cardiac arrhythmia, including torsades de pointes
  - patients with electrolyte disturbances (hypokalaemia or hypomagnesaemia due to the risk of arrhythmia associated with QT interval prolongation)
- consider the potential benefit of treatment against the cardiac risks when prescribing in patients at increased risk of a cardiac event; patients in whom caution is needed are those with:
  - cardiac disease or heart failure
  - conduction disturbances or clinically relevant bradycardia
  - those concomitantly taking other medicines associated with QT interval prolongation
- direct patients to the patient information leaflet and remind at-risk patients of the importance of seeking medical attention if they develop signs or symptoms of a cardiac event
- erythromycin is widely used in children, some of whom may have QT interval prolongation; therefore, consider the child's medical history and balance the treatment benefits against the potential risks
- erythromycin may interact with rivaroxaban and increase the risk of bleeding – consider this interaction when prescribing antibiotics and follow precautions in the product information if concomitant use is necessary
- report suspected adverse drug reactions (ADRs) associated with erythromycin to the Yellow Card scheme

Strengthened warnings for cardiac risks

A European review of safety data has highlighted an increased risk of cardiotoxicity with macrolide antibiotics, particularly erythromycin. Both adverse drug reaction data and the published literature report increased short-term risks of adverse cardiac outcomes associated with erythromycin.

On the basis of these data, the product information for erythromycin will be updated in line with that for clarithromycin to include warnings regarding the risk of QT interval prolongation and fatal arrhythmia.

A new contraindication has been added for those with risk factors for QT interval prolongation and arrhythmia, including for patients with a history of QT interval prolongation or ventricular arrhythmia and patients with electrolyte disturbances. Warnings have also been strengthened on the risk of cardiac events and risk factors. Cardiac arrest and ventricular fibrillation have been added as potential reactions of unknown frequency; however, given the widespread usage they appear to have been reported very infrequently.

Cardiotoxic effects are recognised with other macrolide antibiotics. Clinicians should be aware of the increased short-term risk of adverse cardiac outcomes, so that the benefits and risks of treatment can be fully evaluated at the time of treatment initiation in each patient, particularly those at high risk of cardiac events.

This balance of treatment benefits versus the potential risks should be especially considered in patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances, or clinically relevant bradycardia. Caution should be exercised in patients concomitantly taking other medicinal products associated with QT interval prolongation, and in patients who are elderly since these groups may be more susceptible to drug-associated effects on the QT interval.

Erythromycin is widely used in children, some of who may have QT interval prolongation. We advise healthcare professionals to consider the child's medical history to identify those at risk and to consider the possible risks against the treatment benefits when prescribing erythromycin.

Patients should be informed of the signs and symptoms of cardiac events and be advised to seek medical advice should they occur. Warnings on the signs and symptoms of cardiac events have been added to the patient information leaflet.

Rivaroxaban drug interaction

The European review also concluded that rivaroxaban should be included as an example of a potential interaction between erythromycin and oral anticoagulants in the product information since this interaction could lead to increased risk of bleeding. This interaction is already included in the product information for rivaroxaban (Xarelto).

Erythromycin and clarithromycin inhibit CYP3A4 and P-gp and can lead to an increase in the maximum blood concentration of rivaroxaban. The product information for rivaroxaban advises that the interaction with erythromycin can lead to potential increased bleeding risk in high-risk patients, especially in those with mild or moderate renal impairment.

Rivaroxaban is not the only direct-acting oral anticoagulant (DOAC) to interact with macrolides such as erythromycin. For edoxaban, the product information recommends a reduced dose of 30mg a day for patients on concomitant erythromycin. For dabigatran and apixaban the product information states that concomitant administration of P-gp inhibitors (and for apixaban, also CYP3A4 inhibitors) is expected to result in increased plasma concentrations and that blood concentrations were raised when used concomitantly with another macrolide, clarithromycin.

All patients prescribed DOACs, including those also on macrolides, should be informed of the signs and symptoms of bleeding and be advised to seek medical advice should they occur (see Drug Safety Update from June 2020). Follow guidance on dosing of DOACs in patients with renal impairment and monitor renal function during treatment to ensure dose remains appropriate.

See page 13 for general information about erythromycin and a reminder to report suspected reactions on a Yellow Card

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Erythromycin: update on known risk of infantile hypertrophic pyloric stenosis

Updates have been made to the magnitude of the known risk of infantile hypertrophic pyloric stenosis following exposure to erythromycin in infancy as a result of new epidemiological data. The risk is particularly increased in the first 14 days after birth. Weigh the benefit of erythromycin therapy in infants against the potential risk of infantile hypertrophic pyloric stenosis.

Advice for healthcare professionals:

- an increased risk of infantile hypertrophic pyloric stenosis following exposure to erythromycin in infancy has been reflected in the product information for some time
- data from three recent meta-analyses has led to updates for the magnitude of increased risk with erythromycin use during infancy in general, and to reflect that the risk is highest in the first 14 days after birth
- consider the benefit of erythromycin therapy against the potential risk of developing infantile hypertrophic pyloric stenosis
- advise parents to seek advice from their doctor if vomiting or irritability with feeding occurs in infants during treatment with erythromycin
- report suspected adverse drug reactions (ADRs) to the Yellow Card scheme

New data for risk of infantile hypertrophic pyloric stenosis

Use of the antibiotic erythromycin in infancy has been associated with an increased risk of infantile hypertrophic pyloric stenosis. A recent European review of safety data assessed published literature studies, including data from three meta-analyses[1,2,3] that support an association between exposure to erythromycin in infants and the risk of infantile hypertrophic pyloric stenosis.

Although this risk was already included in the Summary of Product Characteristics (SmPC) for erythromycin medicines, the review recommended that information on the magnitude of the increased risk should be added to the sections on precautions and potential side effects. The background incidence of infantile hypertrophic pyloric stenosis is thought to be 0.1–0.2% livebirths.

The studies show that the risk of infantile hypertrophic pyloric stenosis following exposure to erythromycin is highest in the first 14 days after birth. Available data suggests an incidence of 2.6% (95% CI 1.5 to 4.2) for infants younger than 14 days following exposure to erythromycin.

The studies suggest an overall 2–3-fold increase in risk of infantile hypertrophic pyloric stenosis following exposure to erythromycin in infancy in general. It is noted that the meta-analyses used different age limits to identify studies in infants, with two using a cut-off age for studies of 6 months[1,2] and one using a cut off of 120 days old (around 4 months).[3]

Since erythromycin may be used in the treatment of conditions in infants that are associated with significant mortality or morbidity (such as pertussis or chlamydia), the benefit of erythromycin therapy should be weighed against the potential risk of developing infantile hypertrophic pyloric stenosis. Parents should be informed to contact their doctor if vomiting or irritability with feeding occurs.

1. Murchison L and others. Pediatr Surg Int 2016; 32: 1147–52.

2. Abdellatif M and others. Review Eur J Pediatr 2019; 178: 301–14.

3. Almaramhy HH and others. Ital J Pediatr 2019; 45: 20.

About infantile hypertrophic pyloric stenosis

Infantile hypertrophic pyloric stenosis is characterised by hypotrophy and subsequent narrowing of the pylorus between the stomach and duodenum. Signs and symptoms in infants can include vomiting (sometimes forceful) and irritability after feeding. Treatment is usually pyloromyotomy, a surgical procedure where incisions are made in the muscle walls of the pylorus.

About erythromycin

Erythromycin is a macrolide antibiotic that is active against gram-positive cocci and gram-positive bacilli, some gram-negative cocci and some gram-negative bacilli.

It is widely used to treat chest infections such as pneumonia, skin problems and sexually transmitted diseases. It is used in children, often to treat ear or chest infections.

Erythromycin is licensed for use in both adults and children (including infants and babies).

As for all antibiotic medicines, consideration should be given to official guidance on the appropriate use of antimicrobial agents.

Report suspected reactions on a Yellow Card

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

Reporting suspected ADRs, even those known to occur, adds to knowledge about the frequency and severity of these reactions and can be used to identify patients who are most at risk. Your report helps the safer use of medicines.

Healthcare professionals, patients, and caregivers 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)

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Letters and drug alerts sent to healthcare professionals in November 2020

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Letters

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

- Ondexxya (andexanet alfa): avoid use of andexanet prior to heparinization
- Tecfidera (dimethyl fumarate): updated recommendations in the light of cases of progressive multifocal leukoencephalopathy (PML) in the setting of mild lymphopenia
- Gilenya (fingolimod): updated recommendations to minimise the risk of drug-induced liver injury (DILI)
- Rozlytrek (entrectinib) 100mg and 200mg capsules: missing side effect in EU Patient Information Leaflet
- Solu-Medrone (methylprednisolone as sodium succinate) 40mg powder and solvent for solution for injection: change from lactose-containing to a lactose-free formulation; risk of serious allergic reactions if formulations are confused
- Gliolan (5-aminolevulinic acid, 5-ALA): what to do in case of delayed surgery and information on fluorescence in non-high-grade glioma
- Propofol 10mg/ml (1%) emulsion for injection/infusion: batches with deactivated data in European Medicines Verification System (EMVS)
- Midazolam maleate (Epistatus 10mg in 1ml oromucosal solution, multidose bottle), unlicensed, emergency use medication for prolonged, acute, convulsive seizures: potential risk of incorrectly engaged child-resistant container closures

Drug alerts

Class 4 Medicines Defect Information, Kolanticon Gel 200ml, (PL 17509/0084), EL (20) A/51. Issued 9 November 2020. For one batch of this product, there is a difference in dosage instructions between the carton and label – the Patient Information Leaflet (PIL) and bottle label contain the correct instructions. When dispensing or providing this product, please check batch number and ensure that patients are aware of the correct dosing instructions.

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/52. Issued 11 November 2020. A specific batch is being recalled as a precautionary measure due to some inspected vials showing hairline damage to the shoulder of the vials. Stop supplying the batch immediately and return to supplier.

Class 2 Medicines Recall, Mylan UK Healthcare Ltd, Ancotil 2.5 g/250 ml Solution for Infusion, PL 46302/0116, EL (20) A/53. Issued 12 November 2020. Remaining stock of certain batches is being recalled as a precautionary measure after a product sterility non-compliance during a recent inspection at the contract manufacturing site. Stop supplying the batches immediately and return to supplier.

Class 2 Medicines Recall: Kyowa Kirin Limited, Abstral 200 microgram sublingual tablets, EL (20)A/54. Issued 25 November 2020. Specific batches are being recalled as a precautionary measure due to reports of double tablets in a single-blister pocket. Stop supplying the batches immediately and return to supplier.

Class 2 Medicines Recall: Kent Pharmaceuticals Ltd, Betahistine dihydrochloride 8mg and 16mg Tablets, EL (20)A/55. Issued 26 November 2020. Affected batches are being recalled following contamination with theophylline due to a cross-contamination issue identified with an excipient used in the manufacture of the finished product. Stop supplying the batches immediately and return to supplier.

Class 2 Medicines Recall: Aventis Pharma Limited (t/a Sanofi), Largactil 50mg/2ml Solution for Injection, EL (20)A/56. Issued 26 November 2020. Specific batches of Largactil 50mg/2ml Solution for Injection are being recalled as a precautionary measure due to out of specification results obtained for the impurity chlorpromazine sulphoxide. Stop supplying immediately and return to supplier.

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