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

Volume 12 Issue 8 March 2019

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.

NICE accredited
www.nice.org.uk/accreditation

MHRA is accredited by NICE to provide Drug Safety Update. Further information can be found on the NICE Evidence Search portal: www.evidence.nhs.uk/

To subscribe to monthly email alerts of Drug Safety Update see: https://www.gov.uk/drug-safety-update

First, we inform all healthcare professionals of new restrictions and precautions for use of fluoroquinolone antibiotics following a detailed EU review of very rare reports of disabling and potentially long-lasting or irreversible side effects affecting the musculoskeletal and nervous systems. Healthcare professionals and patients should be vigilant during treatment with fluoroquinolone antibiotics and treatment should be discontinued at the first sign of tendon pain or inflammation (page 2).

Next, read about serious and fatal thromboembolic events reported in association with liposomal irinotecan (Onivyde), authorised for metastatic adenocarcinoma of the pancreas (page 6). Patients should be informed about the signs and symptoms of thromboembolism and be advised to seek medical advice immediate if any occur.

Finally, prescribers of any medicines with teratogenic potential should download, print, and use the new aide-memoire table, which provides guidance on contraceptive methods and the related frequency of pregnancy testing recommended. See page 8 to the advice and page 10 for the table.

On page 11 and 12, we highlight recent letters, drug alerts, and medical device alerts to healthcare professionals. See articles for more.

drugsafetyupdate@mhra.gov.uk

Fluoroquinolone antibiotics: new restrictions and precautions for use due to very rare reports of disabling and potentially long-lasting or irreversible side effects

Disabling, long-lasting or potentially irreversible adverse reactions affecting musculoskeletal and nervous systems have been reported very rarely with fluoroquinolone antibiotics. Fluoroquinolone treatment should be discontinued at the first signs of a serious adverse reaction, including tendon pain or inflammation.

Advice for healthcare professionals:

- systemic (by mouth, injection, or inhalation) fluoroquinolones can very rarely cause long-lasting (up to months or years), disabling, and potentially irreversible side effects, sometimes affecting multiple systems, organ classes, and senses
- advise patients to stop treatment at the first signs of a serious adverse reaction, such as tendinitis or tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling, peripheral neuropathy, and central nervous system effects, and to contact their doctor immediately for further advice – see sheet for patients
- do **not** prescribe fluoroquinolones:
  - for non-severe or self-limiting infections, or non-bacterial conditions
  - for some mild to moderate infections (such as in acute exacerbation of chronic bronchitis and chronic obstructive pulmonary disease; please refer to revised indications in the Summary of Product Characteristics) unless other antibiotics that are commonly recommended for these infections are considered inappropriate (see below)
  - ciprofloxacin or levofloxacin should no longer be prescribed for uncomplicated cystitis unless other antibiotics that are commonly recommended are considered inappropriate (see below)
- avoid use in patients who have previously had serious adverse reactions with a quinolone or fluoroquinolone antibiotic
- prescribe with special caution for people older than 60 years and for those with renal impairment or solid-organ transplants because they are at a higher risk of tendon injury
- avoid use of a corticosteroid with a fluoroquinolone since coadministration could exacerbate fluoroquinolone-induced tendinitis and tendon rupture
- report suspected adverse drug reactions to fluoroquinolone antibiotics on the Yellow Card website or via the Yellow Card app (download it from the Apple App Store, or Google Play Store)

New restricted indications

Fluoroquinolones are antibiotics authorised for serious, life-threatening bacterial infections. As for all antibiotic medicines, consideration should be given to official guidance on the appropriate use of antibacterial agents (see page 4).

EMA's final recommendation on quinolone- and fluoroquinolone-containing medicinal products.

Following an EU-wide review of safety, new restricted indications are being introduced for fluoroquinolone antibiotics available in the UK.

Please refer to the updated Summary of Product Characteristics before prescribing:

- Ciprofloxacin (Ciproxin)
- Levofloxacin
- Moxifloxacin (Avelox)
- Ofloxacin (Tarivid)

Summaries of Product Characteristics will be updated in the coming weeks. In the meantime, see EMA document for exact changes made in indications.

The quinolone nalidixic acid was authorised for urinary tract infections, which is no longer a permitted indication. Therefore, the licence for nalidixic acid has been cancelled.

Fluoroquinolones should not be prescribed for treatment of mild to moderate infections (such as in acute exacerbation of chronic bronchitis and chronic obstructive pulmonary disease) unless other antibiotics that are commonly recommended for these infections are considered inappropriate.

Relevant situations in which other antibiotics may be understood to be inappropriate are those in which there is resistance to the other first-line antibiotics recommended for these infections; when other first-line antibiotics cause side effects that lead to treatment being stopped or the other first-line antibiotics are contraindicated in an individual; or because first-line antibiotics have failed.

Review of disabling and potentially long-lasting, irreversible side effects

The EU review into the benefits and risks of fluoroquinolone and quinolone antibiotics was triggered by reports of disabling and potentially long-lasting, irreversible side effects mainly affecting the musculoskeletal and nervous systems. The review incorporated the views of patients, healthcare professionals, and academics presented at a public hearing in June 2018.

Details and frequency of cases reported

The review identified data for long-lasting adverse reactions associated with quinolone and fluoroquinolone use from spontaneous reports, the scientific literature and non-clinical mechanistic studies. A review of the EMA's EudraVigilance database identified 286 cases of serious adverse reactions reported as disabling and lasting for 30 days or more, without any alternative explanations, from across the EU over a 21-year period. Although cumulative fluoroquinolone patient exposure data are not available for this time period, it is estimated that more than 300 million daily doses of fluoroquinolone antibiotics are dispensed every year in the EU.

Although relatively few cases of these disabling and potentially irreversible adverse reactions have been reported, under-reporting is likely. Due to the seriousness of these reactions sometimes reported in previously healthy people, any decision to prescribe a fluoroquinolone should be taken after a careful assessment of the benefits and risks in each case.

Characteristics of adverse reactions reported and recommendation if tendonitis occurs

Serious side effects reported include tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impaired hearing, vision, taste, and smell. In the musculoskeletal system, tendonitis and tendon rupture were most commonly reported, and in the nervous system paraesthesia was most commonly reported.

Tendon damage (especially to the Achilles tendon but also other tendons) 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.

At the first sign of tendinitis (eg, painful swelling, inflammation), treatment with the fluoroquinolone should be discontinued and alternative treatment should be considered. The affected limb or limbs should be appropriately treated (eg, immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

We have produced a patient sheet to help healthcare professionals to discuss the new measures and actions patients should take.

Precautions for prescribing fluoroquinolones, including for patients at increased risk

Patients who are older than 60 years, have renal impairment, or have had solid-organ transplantation, and those being treated with a corticosteroid are at higher risk of tendon damage. Concomitant treatment with a fluoroquinolone and a corticosteroid should be avoided as the risk of fluoroquinolone-induced tendinitis and tendon rupture may be exacerbated.

Prescribing guidance

Consideration should be given to official guidance on the appropriate use of antibacterial agents. Prescribers should consult NICE and Public Health England's guidance for managing common infections, including upper and lower respiratory, and urinary tract infections. In Scotland, SIGN have also produced antibiotic guidance for prescribers.

The new EU restrictions closely align with existing UK national guidance. The restrictions should not prevent use of a fluoroquinolone for serious or severe infections if this is consistent with UK national guidance or where there are microbiological grounds, and where the benefit is thought to outweigh the risk.

Report suspected adverse drug reactions via the Yellow Card scheme

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

Healthcare professionals, patients, and caregivers can report suspected side effects via the Yellow Card website or via the Yellow Card app. Download the app today via iTunes Yellow Card for iOS devices or via PlayStore Yellow Card for Android devices.

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

Article citation: Drug Safety Update volume 12, issue 8: March 2019: 1.

Onivyde (irinotecan, liposomal formulations): reports of serious and fatal thromboembolic events

Onivyde has been associated with reports of serious thromboembolic events, such as pulmonary embolism, venous thrombosis, and arterial thromboembolism.

Advice for healthcare professionals:

- be aware of reports of serious and fatal cases of thromboembolic events in patients receiving Onivyde for metastatic adenocarcinoma of the pancreas
- a thorough medical history should be obtained in order to identify patients with multiple risk factors in addition to the underlying neoplasm
- advise patients to seek medical advice immediately if signs or symptoms of thromboembolism occur (for example, sudden pain and swelling in a leg or an arm, sudden onset of coughing, chest pain or difficulty breathing)
- report suspected adverse drug reactions (ADRs) to the Yellow Card Scheme – even if the risk is already known, reporting adds to information about the frequency or seriousness of ADRs

Reports of serious thromboembolic events

A routine EU review assessed cases of serious thromboembolic events reported in patients receiving Onivyde. In the cumulative review (October 2015 – April 2018), 23 serious reports of thromboembolic events were identified, of which 4 were fatal. 20 cases of serious thromboembolic events were reported in a 6-month reporting period (October 2017 – April 2018) in the EU.

We have no Yellow Card Reports of this reaction with this formulation in the UK and usage in the UK is very low, however all prescribers should be aware of this risk when using Onivyde.

The reported events included pulmonary embolism, vena cava thrombosis, deep vein thrombosis, catheter site thrombosis, and subclavian vein thrombosis. There were also individual reports of superior vena cava syndrome, portal vein thrombosis, thrombosis, cerebrovascular accident, jugular vein thrombosis, and mesenteric artery thrombosis.

The risk of thromboembolic events has been included in the product information for Onivyde since the time of licensing. However, due to the increased reporting frequency and the seriousness of the reported events, warnings have been added to the Summary of Product Characteristics on the need for a thorough medical history to identify patients with multiple risk factors.

All patients should be informed of the signs and symptoms of thromboembolism and be advised to seek medical advice should they occur. Warnings on the signs and symptoms of thromboembolism have also been added to the Patient Information Leaflet.

About Onivyde (irinotecan, liposomal formulations)
Onivyde is indicated for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in adult patients who have progressed following gemcitabine-based therapy. Onivyde must only be prescribed and administered to patients by healthcare professionals experienced in the use of anti-cancer therapies.

Report any suspected adverse drug reactions
Please continue to report any suspected adverse drug reactions to Onivyde via the Yellow Card Scheme. Your report will help us safeguard public health.

Article citation: Drug Safety Update volume 12, issue 8: March 2019: 2.

Medicines with teratogenic potential: what is effective contraception and how often is pregnancy testing needed?

New guidance on contraceptive methods and frequency of pregnancy testing to reduce inadvertent exposures during pregnancy in a woman taking a medicine of teratogenic potential.

Background

Some medicines are known or suspected to have the potential to increase the risk of birth defects and development disorders (teratogenic potential) when taken during pregnancy, especially during the first trimester (up to week 12 of pregnancy), when a woman may not know she is pregnant. The product information for these medicines advise that pregnancy should be avoided during treatment, with advice on the need to use contraception including, in some cases, formal pregnancy prevention programmes.

When using any medicine with teratogenic potential, a woman should be advised of the risks and encouraged to use the most effective contraceptive method taking into account her personal circumstances.

Contraception

Contraceptive methods are designated as effective or highly effective based on their failure rates in typical use in the first year.[1] 'Typical use' includes user error (for example, missed pills, starting a pack late) or use in circumstances that decrease efficacy such as interactions with concomitant medicines.

Highly effective methods have typical-use failure rates of less than 1% and include male or female sterilisation and long-acting reversible contraceptive (LARC) methods (intrauterine devices and implants).

Progestogen-only injections have a typical-use failure rate of 6%, but this may be due to repeat injections being administered late. Progestogen-only injections may be considered as highly effective if repeat injections are documented as having been administered on schedule by a healthcare professional.

Other methods described as effective include combined hormonal contraceptive (pills, patches, or vaginal rings) and progestogen-only pills, which have typical-use failure rates of 9%.

Methods used at time of sexual intercourse or based on fertility awareness have higher typical-use failure rates and are not classed as 'effective' for use with medicines with teratogenic potential so should not be relied upon alone.

Need for pregnancy testing

A woman may be unaware she is pregnant at the start of treatment or be in the early stages of pregnancy at the time of repeat prescribing due to contraceptive failure. The MHRA continues to receive reports of inadvertent exposure to such medicines during early pregnancy. One way to avoid inadvertent exposures is for a pregnancy test to be performed before prescription of a medicine with teratogenic potential.

Download, print, and use new table

The Medicines for Women's Health Expert Advisory Group of the Commission on Human Medicines has developed an aide-memoire table to provide guidance to prescribers of medicines with teratogenic potential on the frequency of pregnancy testing needed to avoid exposure in pregnancy during treatment, depending on the chosen contraceptive method. The aide-memoire table provides a summary of the pregnancy testing advice for the most common contraceptive methods. The table is colour-coded according to the most reliable methods. It is available to download and print, so can be used as a poster in clinics and to update local guidance, as needed. It is also included on page 10.

Key considerations used in preparing the guidance

The guidance is based on the following considerations:

- The likelihood of pregnancy is not constant and can vary with changes in a woman's circumstances during treatment. Therefore, the likelihood of pregnancy should be assessed before each prescription of a medicine with known teratogenic potential
- Pregnancy tests may not detect an early pregnancy that has occurred after unprotected sex in the preceding 3 weeks. Therefore, women should have a repeat pregnancy test 3 weeks after starting a new contraceptive method if there was any risk of pregnancy at the start of the contraceptive method, even if the first test was negative
- Modern contraceptive methods have low failure rates (0.03–0.6%) when used reliably and consistently ('perfect use'), but failure rates are substantially higher for some methods because of user error or interactions with concomitant medicines ('typical use'). Risk of user error is higher for daily methods than for long-acting reversible contraceptive (LARC) methods and is highest for methods used at time of sexual intercourse
- Choice of contraceptive method is an individual one and can depend on a number of clinical factors as well as the woman's personal preference (see current clinical guidance on contraception and statement on teratogenic drugs from the Faculty of Sexual and Reproductive Health [FSRH]). However, different methods have different typical-use failure rates and durations of action, which can affect the frequency of pregnancy testing required

If pregnancy cannot be excluded, the decision to start or continue treatment with a medicine with teratogenic potential will depend on individual circumstances, such as the urgency for treatment and alternative treatment options. If feasible, treatment with a medicine with teratogenic potential should be delayed until pregnancy has been excluded by a repeat test.

Source of guidance

This guidance was produced by the MHRA in consultation with advisory committees the Commission on Human Medicines and Medicines for Women's Health Expert Advisory Group.

Recommendations are based on FSRH statement on teratogenic drugs and contraceptive failure rates in typical use.[1]

1. Trussell J. Contraceptive failure in the United States. Contraception 2011; 83: 397-404.

Article citation: Drug Safety Update volume 12, issue 8: March 2019: 3.

Pregnancy testing and contraception for pregnancy prevention during treatment with medicines of teratogenic potential

- **Risk of pregnancy should be assessed prior to each teratogen prescription**
  - Risk of pregnancy may be high at start of a method or when switching between methods due to risk of pregnancy from unprotected sex prior to starting the method, unreliable use of the previous contraceptive method, and/or time needed to establish contraceptive efficacy at the start of the new method.
  - Pregnancy tests at start of contraceptive method may not detect an early pregnancy following unprotected sex in the last three weeks;
- **Any starter on new method contraception should have a repeat pregnancy test at 3 weeks if there is any risk of pregnancy at start of contraceptive method**
- The duration of teratogen prescriptions may need to be shortened for patients who use contraceptive methods that require frequent pregnancy testing

Effectiveness of contraceptive in typical use[1]	Contraceptive method	Duration contraceptive method used / other situations	Pregnancy test needed before next teratogen prescription?
Highly effective methods **(Typical use failure rates less than 1%)**	Copper intrauterine device (copper IUD)	Established user more than 3wks to 5-10 yrs (depending on IUD[2])	No
	Levonorgestrel-releasing intrauterine system (LNG-IUS)	Established user more than 3wks to 3-5 yrs (depending on IUS[2])	No
	Progestogen Implant	Established user more than 3wks to 3yrs	No
		Established user (more than 3wks), but concurrent use of interacting medicines which may affect efficacy[3]	Yes + review / refer for contraceptive advice
Effective methods **(Typical use failure rates greater than 1%)** **Additional barrier methods are advised during teratogen use**	Depot medroxyprogesterone acetate (DMPA) subcutaneous (SC) or intramuscular (IM) injections[4]	Established user (more than 3wks + repeat injections on schedule) and less than 13 wks since last injection + documented as administered by healthcare professionals	No
		Established user (more than 3wks + repeat injections on schedule and less than 13 wks since last injection) but self-administered or undocumented administration	Yes, test if any suspected risk of pregnancy
		More than 13 wks since last injection (ie beyond recommended duration of use of last injection)	Yes + review / refer for contraceptive advice
	Combined hormonal contraceptives (pills, patches or vaginal ring) or progestogen-only pills	Established user (more than 3wks), reliable and consistent use	Yes, test if any suspected risk of pregnancy
		Established user (more than 3wks) but with unreliable or inconsistent use of method, eg: • missed pills, late patch • Diarrhoea or vomiting; • use of other interacting medicines that may affect efficacy[3]	Yes + review / refer for contraceptive advice
	Other methods or no contraception	Any duration of use of other methods	Yes + review / refer for contraceptive advice;
		No contraception	Assess need for contraception + test if any suspected risk of pregnancy + review / refer for contraceptive advice;

Explanatory notes:

1. Effectiveness of methods are based on failure rates in typical use (which includes risk of user error) rather than perfect use. Perfect use failure rates are similar for specific methods listed (0.03 – 0.6%) but risk of user error is higher for daily methods than for long acting reversible contraceptive (LARC) methods and are highest for methods used at time of sexual intercourse. Highly effective methods are based on less than 1% failure rate in typical use; Less effective methods are based on greater than 1% failure rate (6 – 9%) in typical use (Trussell J Contraceptive failure in the United States Contraception. 2011 May;83(5):397-404. doi: 10.1016/j.contraception.2011.01.021. Epub 2011 Mar 12)
2. Refer to Product Information for specific products; patients should be reviewed / referred for contraception advice at the end of the recommended duration of use
3. Implants are only considered as highly effective and combined hormonal contraceptives and progesterone-only pills are only considered as effective if interactions with any concurrent medicine are not a concern (see FSRH guidance on drug interactions with hormonal contraception)
4. DMPA (IM or SC) injection can be considered as highly effective if it is administered by healthcare professionals and continuous repeat use is documented as occurring within recommended duration of action (equivalent to perfect use, failure rate = 0.2%). Otherwise it is considered an effective contraceptive (typical use failure rate =6%). The same rationale should be used for other injection products with different recommended duration of action (eg Norethisterone Enanthate)

MHRA Regulating Medicines and Medical Devices

Letters and drug alerts sent to healthcare professionals in February 2019

The following letters were sent to healthcare professionals:

- **Vyxeos (cytarabine, daunorubicin): temporary interruption of UK packaging**; provide English-language patient information leaflets with imported Nordic batches

- **OZURDEX® 700 micrograms intravitreal implant (dexamethasone)**: Update on silicone particle issue: Supply of new (defect-free) stock and recall of remaining stock in the market

.

Irbesartan recall

You should also be aware of a European-level recall from pharmacies of certain batches of Actavis irbesartan-containing products as a precautionary measure due to possible contamination with N-nitrosodiethylamine (NDEA). See the recall notice on the MHRA website (issued 13 February 2019).

Advice for healthcare professionals:

- stop supplying the affected products/batches listed immediately; quarantine all remaining stock and return it to your supplier using your supplier's approved process
- advise patients not to stop taking their medication as the risk of discontinuing the medicine is higher than the potential risk presented by the contaminant. A treatment review is not necessary until the next routine appointment.
- although shortages of irbesartan-containing products are not anticipated, there may be some local supply issues – should this be the case, patients should be advised to speak to their doctor to discuss alternative treatments

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

Other drug alerts

- **Class 4 defect information: Amoxicillin 500mg Capsules BP (MDR 92-12/18).** Issued 4 February 2019. A change to the Patient Information Leaflet (PIL) for this product has not been implemented by the required timeline. The change concerns the addition of the symptoms of a potential side effect, 'Drug Reaction with Eosinophilia and Systemic Symptoms' (DRESS), which is a potentially life-threatening condition. If dispensing a batch listed in the alert, healthcare professionals are requested to remove the PIL in the pack and provide a copy of the correct version, which can be downloaded here.

- **Class 4 defect information: Atropine Sulfate 3mg/10ml Solution for injection in pre-filled syringe. (MDR 18-01/19).** Issued 18 February 2019. There is an error in the Patient Information Leaflet (PIL) for batches of Atropine Sulfate 3 mg/10 ml Solution for injection in pre-filled syringe.

- **Drug Alert Class 4: Paracetamol Infusion, Accord. (MDR 07-02/19).** Issued 28 February 2019. There is an error on the portion of the Patient Information Leaflet (PIL) for the Paracetamol Infusion intended for healthcare professionals. This error relates to an unmarketed presentation in the UK. The corrected PIL can be accessed here.

Article citation: Drug Safety Update volume 12, issue 8: March 2019: 4.

Medical Device Alerts issued in February 2019

In this monthly update, we highlight selected Medical Device Alerts that have been issued recently by MHRA. Please note, this is not an exhaustive list of medical device alerts. For all Medical Device Alerts from MHRA, see Alerts and recalls for drugs and medical devices.

The following alerts were recently issued:

- **enFlow IV fluid and blood warmer - risk of unsafe levels of aluminium leaching from the device (MDA/2019/015).** Published 8 March 2019. Manufactured by Vyaire – Cartridges with an aluminium warming plate in the fluid pathway can lead to an IV infusion containing aluminium above currently recommended safe levels. An alternative fluid warming device should be used if available. If no alternative is available, a local risk assessment should be done and documented based on a clinical risk-benefit analysis before using this fluid warmer.
- **Implantable cardiac pacemakers: specific brands of dual chamber pacemakers - risk of syncope due to pause in pacing therapy (MDA/2019/008)**. Issued 13 February 2018. Manufactured by Medtronic Inc – a subset of dual chamber pacemakers may experience a loss of pacing therapy when programmed to a dual chamber mode with atrial-sensing (MDA/2019/008).
- **Accu-Chek® Insight insulin pumps – some need to be fitted with key frames to reduce the risk of accidentally unlocking keys or pressing the bolus buttons**. Issued 19 February 2019. Manufactured by Roche Diabetes Care – Important instructions on how to fit 2 separate key frames to prevent accidentally activating the pump (MDA/2019/009).
- **Professional use monitor/defibrillator: LIFEPAK 15 – risk of device failure during patient treatment and possible failure to deliver therapy**. Issued 20 February 2019. Manufactured by Stryker – potential for a lock-up condition where the device becomes non-responsive after a defibrillation shock has been delivered.

Article citation: Drug Safety Update volume 12, issue 8: February 2019: 5.