Medicines & Healthcare product Regulatory Agency

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 16 Issue 2 September 2022

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 ask prescribers and dispensers of long-acting (prolonged-release) formulations of methylphenidate for the treatment of ADHD to use caution if switching patients between products as different instructions for use and different release profiles may affect symptom management.

On page 6, we note that the third-line treatment indication of rucaparib, for female genitourinary cancers, has been withdrawn following review of the findings of ARIAL-4, which showed lower overall survival for rucaparib versus standard chemotherapy. This advice does not affect use of rucaparib in maintenance of patients who are in response (complete or partial) to platinum-based chemotherapy.

On page 8, we summarise recent advice relating to COVID-19 vaccines and medicines published since the August 2022 issue of Drug Safety Update. And on page 10, we include recent letters, recalls, and notifications sent to healthcare professionals about medicines.

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Methylphenidate long-acting (modified-release) preparations: caution if switching between products due to differences in formulations

Prescribers and dispensers should use caution if switching patients between different long-acting formulations of methylphenidate (Concerta XL, Medikinet XL, Equasym XL, Ritalin LA, and generics) as different instructions for use and different release profiles may affect symptom management.

Advice for healthcare professionals:

- caution should be used if long-acting formulations of methylphenidate are to be used interchangeably due to the differences between formulations in dosing frequency, administration with food, amount and timing of the modified-release component, and overall clinical effect
- follow specific dosage recommendations for each formulation
- if considering a switch to another long-acting preparation:
    - consult with the patient (and their parent or caregiver if relevant) to discuss the reasons for this and the possible changes they may experience in symptom management and side effects (and what to do if these occur)
    - consider patient preferences such as their individual needs, dose frequency, possible side effects, or other issues related to the patient's condition
    - reiterate the instructions for use for the newly prescribed formulation, especially whether it should be taken with or without food
- clinical guidance advises to prescribe these long-acting formulations of methylphenidate by specifying brand name or by using the generic drug name and name of the manufacturer
- report any suspected adverse drug reactions associated with methylphenidate or other medicines on a Yellow Card

Advice to provide to patients or caregivers:

- there are differences between long-acting methylphenidate medicines in how they release the medicine to manage ADHD symptoms and in the instructions on how to take them
- we have asked doctors and pharmacists to be cautious when switching patients between different long-acting formulations of methylphenidate
- carefully read and follow the advice in the Patient Information Leaflet that comes with your medicine and speak to a healthcare professional if you are concerned about side effects or are concerned about your child's health or medicines
- it is especially important to follow advice on how much methylphenidate to take and to follow instructions on when and how to take it – these can affect how well the medicine works for your ADHD

About methylphenidate

Methylphenidate is used as part of a comprehensive treatment programme for attention deficit hyperactivity disorder (ADHD) in children and adolescents aged between 6 and 18 years and in adults. It is authorised only after other treatment measures, such as counselling and behavioural therapies, have proven insufficient to manage symptoms.

Methylphenidate is available in the UK in immediate-release and long-acting formulations taken orally (tablets or capsules). Long-acting medicines are those labelled as prolonged-release, modified-release, or sustained-release formulations.

Review and updates to advice

A recent European procedure looked at differences between Medikinet XL and other long-acting formulations of methylphenidate and the impact on safety and efficacy when switching to and from products. This procedure concluded that caution is advised if long-acting formulations of methylphenidate are used interchangeably due to the differences between formulations in frequency of dosing, administration with food, and plasma drug concentration achieved.

These updates will be made to the UK Summary of Product Characteristics (SmPC) for Medikinet XL. We have considered this, together with the safety data for all long-acting methylphenidate medicines, and agree with this position.

We also considered reports and queries from patients, carers, and healthcare professionals in the UK regarding concerns of lack of effect and increased adverse effects when switching between long-acting formulations of methylphenidate. We sought the views of the Paediatric Medicines Expert Advisory Group of the Commission on Human Medicines on these concerns.

We are alerting healthcare professionals to the need to use caution when prescribing or dispensing long-acting methylphenidate preparations and to adequately counsel patients as required. We will continue to monitor safety information and will seek to introduce this wording in other long-acting methylphenidate formulations as appropriate.

We note this advice is consistent with existing clinical guidance from the Specialist Pharmacy Service on prescribing modified-release methylphenidate preparations by brand.

Information on how formulations differ

All long-acting methylphenidate preparations include an immediate-release component as well as a modified-release component. This means methylphenidate is released in two phases (biphasic). This allows for rapid onset of action and a slower extended release, avoiding the need to take further doses during the day to maintain effect. It is possible that several formulations will need to be tried before one is found that suits an individual.

The biphasic-release profiles of these products are not all equivalent and contain different proportions of the immediate-release and modified-release components. The differing time–action profiles provided by long-acting formulations of methylphenidate allow clinicians to target specific periods of the day that are particularly relevant for a patient, facilitating individualisation of ADHD treatment. Transferring to another formulation can result in changes in symptom management at key time periods during the day.

The response to methylphenidate varies greatly from patient to patient and therefore the doctor will need to increase or decrease a dose to find one that suits the patient (dose-finding phase). A number of long-acting methylphenidate preparations are available, Medikinet XL, Ritalin LA, Equasym XL, Concerta XL and generics, and they differ from each other in several aspects, including:

- their available dose strengths
- the ratio of immediate-release and modified-release methylphenidate
- mechanism of release
- pharmacokinetics
- plasma concentration-time profiles and bioavailability
- their dependence on the presence or absence of food at the time of ingestion

Due to these differences, changing preparations means that the dose may have to be adjusted to avoid the potential for overdose or underdose.

Advice on switching of methylphenidate products

Switching between different preparations may result in concerns from patients and parents or caregivers.

No single formulation meets the requirements of all patients with ADHD and the unique characteristics of each agent should be matched to the individual needs of the patient. Switching between formulations with differing pharmacokinetics can also be associated with differences in adverse events or patient experiences of ‘effectiveness’ in both paediatric and adult patient groups.

Frequent switching between different products should be avoided. Once a patient is established on a product, prescribers may wish to maintain them on that specific product. In such cases, prescribing by specifying brand or manufacturer may be appropriate. This is consistent with existing guidance from the Specialist Pharmacy Service and in the BNF and BNF for Children.

Changes to medication should only be made in the context of individual review and should be communicated to patients, who should be advised to report any changes to their symptoms or development of side effects.

Report suspected adverse drug 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 timing, treatment dates, and product brand name.

Report suspected side effects to medicines, vaccines, medical devices, and test kit incidents used in coronavirus (COVID-19) testing and treatment 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 16, issue 2: September 2022: 1.

Rucaparib (Rubraca▼): withdrawal of third-line treatment indication

The third-line treatment indication for rucaparib has been withdrawn following a review of the findings of the ARIEL-4 trial, which showed lower overall survival for rucaparib treatment versus standard chemotherapy in patients with high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer.

Advice for healthcare professionals:

- final analysis of the ARIEL-4 study findings showed lower overall survival with rucaparib versus standard chemotherapy control in the treatment of relapsed, BRCA-mutated, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer
- rucaparib should no longer be used for third-line cancer treatment in new patients
- inform patients already receiving rucaparib for the third-line treatment indication of the latest data and recommendations (see letter for healthcare professionals), and consider other treatment options
- this advice does not affect use of rucaparib in maintenance of patients who are in response (complete or partial) to platinum-based chemotherapy
- continue to report any suspected adverse reactions to black triangle medicines such as Rubraca to the Yellow Card scheme

Conclusion of review of benefits and risks

Rucaparib is a Poly(ADP-Ribose) Polymerase (PARP) inhibitor used for high-grade cancers of the ovary, fallopian tubes, and the peritoneum. It targets cancer cells with mutations in the BReast CAncer (BRCA) genes. Rucaparib was granted a conditional approval in 2018, pending the ARIEL-4 study confirming its safety and effectiveness in the third-line treatment indication.

The ARIEL-4 study compared outcomes for rucaparib versus chemotherapy in treatment of patients whose cancer had relapsed after at least 2 previous treatments and who were still eligible for further chemotherapy. The final analysis showed lower overall survival with rucaparib versus chemotherapy (19.4 months versus 25.4 months, respectively, hazard ratio of 1.31 (95% CI 1.00 to 1.73; p=0.0507)).

A European review of these findings has recommended withdrawal of the third-line treatment indication since the benefits of Rubraca when used in this indication had not been confirmed and treatment may be associated with an increased risk of death. The MHRA has reviewed the recommendation and agreed with this removal of indication in the UK. See letter to UK healthcare professionals.

We understand that use of this medicine in the UK is very low. Patients who are concerned should discuss with their cancer care team or cancer specialist.

Report on a Yellow Card

Rucaparib (Rubraca▼) is a black triangle medicine and all suspected adverse drug reactions should be reported to the Yellow Card scheme.

Report 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 timing, 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 16, issue 2: September 2022: 2.

COVID-19 vaccines and medicines: updates for September 2022

Recent information relating to COVID-19 vaccines and medicines that has been published since the August 2022 issue of Drug Safety Update, up to 23 September 2022.

Approval of Pfizer/BioNTech bivalent COVID-19 booster vaccine

We have approved the Pfizer/BioNTech bivalent COVID-19 Vaccine as a booster after it was found to meet our standards of safety, quality and effectiveness. The brand name for the bivalent vaccine is Comirnaty Original/Omicron BA.1.

The updated booster vaccine targeting the original coronavirus strain and the Omicron BA.1 variant, has been approved for use in individuals aged 12 years and above. This decision has been endorsed by the Commission on Human Medicines, after a careful review of the evidence.

Safety monitoring in clinical trials showed that the types of side effects observed were the same as those seen for the original Pfizer/BioNTech monovalent vaccine (brand name Comirnaty) booster dose and were typically mild and self-resolving, and no new serious safety concerns were identified.

Please see the Press Release and the Decision page for more information about Pfizer/BioNTech bivalent Original/Omicron booster vaccine.

MHRA statement: COVID-19 vaccines are safe and effective during pregnancy and breastfeeding

We would like to reassure the public that our advice has not changed. Our advice remains that the COVID-19 vaccines are safe and effective during pregnancy and breastfeeding and there is substantial evidence to support this advice.

For our latest advice, please see our Summary of Coronavirus Yellow Card Reporting or the relevant Summary of Product Characteristics.

Summaries of Yellow Card reporting

We continue to publish the summaries of the Yellow Card reporting for the COVID-19 vaccines being used in the UK. The report summarises information received via the Yellow Card scheme and includes other data such as usage of COVID-19 vaccines and relevant epidemiological data. The report is updated regularly to include other safety investigations carried out by the MHRA under the COVID-19 Vaccine Surveillance Strategy.

Other recent MHRA updates on Coronavirus vaccines and medicines:

We have also recently:

- granted an extension to the Nuvaxovid COVID-19 Vaccine manufactured by the company Novavax to allow use in 12 to 17 year olds
- updated the Summary of Product Characteristics and Patient Information Leaflet for Comirnaty monovalent COVID-19 Vaccine (Pfizer/BioNTech) to include information about receiving a heterologous booster dose in individuals aged 18 years and over, and to update information on shelf life and transportation storage time

See guidance on COVID-19 for all our latest information, including after publication of this article.

We previously included summaries of latest COVID-19 information, including in the June 2022, July 2022 and August 2022 issues of Drug Safety Update.

Reporting Yellow Cards

Report suspected side effects to medicines, vaccines and medical devices and test kit incidents used in coronavirus (COVID-19) testing and treatment using:

- the dedicated Coronavirus Yellow Card reporting site
- the Yellow Card app (download from the Apple App Store or Google Play Store)

For products under additional monitoring such as the COVID-19 vaccines, you should report all suspected adverse side effects. This will allow the MHRA to identify new safety information for these products.

When reporting please provide as much information as possible, including information about medical history, any concomitant medications, onset timing, and treatment dates, and for vaccines, the product brand name and batch number.

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

If you have been forwarded this article, subscribe directly to Drug Safety Update via our website.

Article citation: Drug Safety Update volume 16, issue 2: September 2022: 3.

Letters and medicine recalls sent to healthcare professionals in August 2022

Letters

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

- Rubraca (rucaparib): restriction of indication – see accompanying Drug Safety Update article on page 2
- Comirnaty ▼30 micrograms/dose concentrate for dispersion for injection (tozinameran), COVID-19 mRNA Vaccine (nucleoside modified): important shelf-life update for Great Britain and Northern Ireland
- Spikevax▼ COVID-19 mRNA Vaccine (nucleoside modified): important shelf-life update when stored at ultra-low-temperature conditions

Medicine Recalls and Notifications

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

National Patient Safety Alert: Class 1 Medicines Recall Notification: Recall of Mexiletine hydrochloride 50mg, 100mg and 200 mg Hard Capsules, Clinigen Healthcare Ltd, due to a potential for underdosing and/or overdosing, NatPSA/2022/007/MHRA. Issued 4 August 2022. Batches of mexiletine hydrochloride 50mg, 100mg and 200mg hard capsules are being recalled due to a due to a potential risk of underdose or overdose that could have consequences for the safety of patients. Please see the national patient safety alert notice for more information and actions to take.

Company led medicines recall: Stockport Pharmaceuticals, Sodium Chloride Eye Drops 5% 1x10ml (unlicensed medicine), CLMR (22)A/06. Issued 8 August 2022. A batch of Sodium Chloride Eye Drops 5% w/v 1x10ml (unlicensed medicine) is being recalled as the sterile eye droppers supplied with this product are expired. Stop supplying the batch immediately, quarantine all remaining stock and return to the company.

Class 2 Medicines Recall: Sun Pharmaceutical Industries Europe BV, Zoledronic acid SUN 5mg solution for infusion, EL(22)A/34. Issued 11 August 2022. Batches of Zoledronic acid SUN 5mg solution for infusion are being recalled as a precaution due to out of specification results observed for Particulate Matter Test during routine stability testing. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

Class 4 Medicines Defect Information, Rosuvastatin 5 mg, 10 mg and 20 mg film-coated tablets EL (22)A/35. Issued 17 August 2022. Further batches of Rosuvastatin 5mg, 10mg and 20mg film-coated tablets have been identified to contain Patient Information Leaflets omitting the latest safety information on medicine interactions and possible side effects. Healthcare professionals are advised to exercise caution when dispensing the product and asked to provide an updated Patient Information Leaflet where possible.

Class 2 Medicines Recall: Dysport 500 Units Powder for Solution for Injection, EL(22)A/36. Issued 22 August 2022. A batch of Dysport (clostridium botulinum type A toxin-haemagglutinin complex) 500 Units Powder for Solution for Injection has been identified as a falsified medicine and is being recalled. Stop supplying the above falsified batch immediately, quarantine all remaining stock and return it to your supplier for onward investigation.

Class 2 Medicines Recall: Hikma Pharmaceuticals USA Inc, Lorazepam 2mg/ml Injection, Lorazepam 4mg/ml Injection (unlicensed medicines) EL(22)A/37. Issued 30 August 2022. Batches of Lorazepam 2mg/ml and 4mg/ml Injection (unlicensed medicine) are being recalled due to an out of specification result with related substances during testing. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

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

Sign-up to receive MHRA alerts about drugs and medical devices and subscribe to Drug Safety Update.

Clinical Practice Research Datalink studies: DaRe2THINK and ASMPTOMATIC trials for GP practices

Clinical Practice Research Datalink (CPRD, part of the MHRA) is a real-world research service to support public health and clinical research projects. CPRD collects anonymised patient data to inform clinical guidance and best practice. All GP practices across the UK that use EMIS, SystmOne, and Vision clinical IT systems are encouraged to sign up to CPRD for free practice-level quality improvement reports and to take part in optional research studies.

CPRD is currently recruiting GP practices using EMIS IT systems to take part in 2 trials to benefit patients:

- The *DaRe2THINK trial* is investigating if early intervention with direct oral anticoagulants can reduce the risk of cognitive decline and vascular dementia in patients with atrial fibrillation
- The ASYMPTOMATIC trial is aiming to find the best treatment for children with mild asthma by investigating whether only using a preventer inhaler when a child has asthma symptoms is as effective as using a preventer inhaler every day.

For more information and to sign up, please see the CPRD webpage or contact GPnetwork@mhra.gov.uk

Article citation: Drug Safety Update volume 16, issue 2: September 2022: 4.