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 of new recommendations for 5-fluorouracil and related medicines to minimise the risk of life-threatening toxicity in patients with dihydropyrimidine dehydrogenase (DPD) deficiency. For the oncology medicines 5-fluorouracil (intravenous), capecitabine, and tegafur (page 2), testing for DPD deficiency should be carried out before initiation of treatment. For flucytosine (page 5), indicated for systemic yeast and fungal infections, pre-treatment testing for DPD is not required, but determination of DPD activity should be considered in cases of severe toxicity.

On page 7, we alert prescribers to reports of severe hypertension (including rare cases of hypertensive crisis) and rare cases of posterior reversible encephalopathy syndrome with the oncology medicine niraparib, particularly in early treatment. New blood pressure monitoring requirements are in place.

Next, see updated safety recommendations for the HIV medicine dolutegravir following continued evaluation of studies assessing risk of neural tube defects with use in pregnancy. Previously communicated restrictions against use in pregnancy are no longer in place but we ask prescribers to discuss with women of the potential for neural tube defects and the benefits and the risks of continuing treatment if planning a pregnancy.

On page 11, we link to recent MHRA advice to healthcare professionals regarding the safe use of warfarin and other anticoagulants during the coronavirus (COVID-19) pandemic.

Finally, on page 13, read how you can support #MedSafetyWeek (2–8 November 2020).

5-fluorouracil (intravenous), capecitabine, tegafur: DPD testing recommended before initiation to identify patients at increased risk of severe and fatal toxicity

Patients with complete or partial dihydropyrimidine dehydrogenase (DPD) deficiency are at increased risk of severe and fatal toxicity during treatment with these medicines. All patients should be tested for DPD deficiency before initiation to minimise the risk of these reactions.

Advice for healthcare professionals:

- patients with complete or partial dihydropyrimidine dehydrogenase (DPD) deficiency are at increased risk of severe and fatal toxicity during treatment with medicines containing 5-fluorouracil (intravenous), capecitabine, and tegafur
- DPD deficiency is most often caused by inherited variants of the *DYPD* gene
- test all patients for DPD deficiency before initiation of treatment with these products
- ask patients whether they or their family members have history of complete or partial DPD deficiency
- do not treat patients with known complete DPD deficiency with these medicines
- for patients with partial DPD deficiency, consider a reduced starting dose
- monitor all patients for toxicity particularly during the first cycle of treatment or after a dose increase
- advise patients that despite negative test results for DPD deficiency, severe toxicity may still occur and ensure they have a copy of the patient information leaflet
- report suspected adverse drug reactions associated with medicines to the Yellow Card scheme

Review of DPD testing prior to treatment

Fluoropyrimidines are a group of anti-cancer medicines including 5-fluorouracil and its prodrugs capecitabine and tegafur – see Background section on page 4.

The *DPYD* gene encodes dihydropyrimidine dehydrogenase (DPD), a key enzyme involved in catabolism of 5-fluorouracil. DPD deficiency is most often caused by inherited variants of the *DYPD* gene. Treatment of patients with DPD deficiency with these medicines increases risk of serious and fatal toxicities (see Characteristics of reactions on page 3).

EMA. 'Public Assessment Report. 27 March 2020.

Complete DPD deficiency is rare (0.01–0.5% of Caucasian people), but partial DPD deficiency is estimated to affect 3–9% of Caucasian people.[1] Most data on the frequency of DPD deficiency are in Caucasian people and rates may differ in other ethnic groups.

A recent European safety review has recommended that, despite uncertainties in the optimal pre-treatment testing methodologies, all patients should undergo testing for DPD deficiency prior to the initiation of these treatments. A letter has been sent to healthcare professionals to inform of these requirements. Safety warnings will also be updated in the Summary of Product Characteristics and Patient Information Leaflets (product information).

The review also considered and made recommendations for flucytosine, indicated for severe systemic fungal infections - see page 5.

Fluorouracil is also available in topical formulations. Due to very low systemic absorption via this route, DPD testing is not required prior to initiation of topical treatment. For topical 5-fluorouracil (5%), if systemic drug toxicity is confirmed or suspected, determination of DPD activity should be considered in line with existing UK product information.

Characteristics of reactions

DPD activity is rate limiting in the catabolism of 5-fluorouracil. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidines-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia, and neurotoxicity.

DPD-deficiency-related toxicity usually occurs during the first cycle of treatment or after dose increase.

Treatment considerations in patients with DPD deficiency

Patients with complete DPD deficiency are at high risk of life-threatening or fatal toxicity and must not be treated systemically with fluoropyrimidines.

Patients with partial DPD deficiency are at increased risk of severe and potentially life-threatening toxicity. A reduced starting dose should be considered to limit the risk of severe toxicity. DPD deficiency should be considered as a parameter to be taken into account in conjunction with other routine measures for dose reduction. Initial dose reduction may impact the efficacy of treatment and so, in the absence of serious toxicity, subsequent doses may be increased with careful monitoring.

Despite negative test results for DPD deficiency, severe toxicity may still occur and patients should be counselled on the benefits and risks of their cancer treatments and provided with the patient information leaflet.

Reports in the UK

Up to 17 June 2020, the Yellow Card scheme has received 30 reports associated with a fatal outcome that describe a known or suspected DPD deficiency with fluorouracil and capecitabine. These include reports of testing and confirmation of DPD deficiency after patients were treated with capecitabine and developed severe and fatal toxicity.

Caution should be exercised in interpreting the Yellow Card data as they may be affected by under-reporting.

Genotyping and phenotyping

Consider clinical and other applicable guidelines before starting patients on these medicines.

The European review considered that pre-treatment genotype testing for mutations of the DPYD gene can identify patients with DPD deficiency. The review described four DPYD variants that can cause complete absence or reduction of DPD enzymatic activity (see details of specific genotype advice in the amended product information). However, other rare variants may also be associated with an increased risk of severe or life-threatening toxicity.

Data on the frequency of the four DPYD variants in populations other than Caucasian people are limited but their frequency is considered to vary between different ethnic groups.

The European review recommended that phenotyping can also be used to test for DPD deficiency through the measurement of pre-therapeutic blood levels of the endogenous DPD substrate uracil in plasma. There are uncertainties regarding uracil thresholds to define complete and partial DPD deficiency, however, indicative blood uracil cut-off levels are provided in the amended product information for these medicines.

Therapeutic drug monitoring of continuous 5-fluorouracil infusions

The European review considered that complementary to DPD deficiency testing before initiation of treatment, therapeutic drug monitoring of 5-fluorouracil may improve clinical outcomes in patients treated with continuous 5-fluorouracil infusions by reducing toxicities and improving efficacy. The target area under the curve (AUC) is between 20 and 30 mg x h/L.

Background

These measures affect the following medicines:

- Parenteral 5-fluorouracil: a component of the standard therapy for a variety of malignancies, including colorectal, pancreatic, gastric, breast and head and neck cancer, mostly used in combination with other anticancer agents

- Capecitabine: an oral prodrug of 5-fluorouracil, indicated for the treatment of colorectal, gastric and breast cancer

- Tegafur: an oral prodrug of 5-fluorouracil, available in combination with two modulators of 5-fluorouracil metabolism, gimeracil, and oteracil for the treatment of gastric cancer

Report on a Yellow Card

Please report suspected serious adverse drug reactions (ADRs) associated with medicines containing 5- fluorouracil, capecitabine or tegafur to the MHRA via 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 medical history, any concomitant medication, onset, treatment dates, and product brand name.

Article citation: Drug Safety Update volume 14, issue 3: October 2020: 1.

Flucytosine (Ancotil): new contraindication in patients with DPD deficiency

Flucytosine is a prodrug of 5-fluorouracil used to treat systemic yeast and fungal infections and can cause life-threatening and severe toxicity in patients with complete and partial dihydropyrimidine dehydrogenase (DPD) deficiency. Although pre-testing of DPD status before flucytosine treatment is not required, a new contraindication for patients with complete DPD deficiency has been introduced.

Advice for healthcare professionals:

- flucytosine should not be used in patients with known complete dihydropyrimidine dehydrogenase (DPD) deficiency due to the risk of life-threatening toxicity
- patients with a partial DPD deficiency are also at increased risk of severe toxicity
- do not delay antimycotic therapy with flucytosine for pre-treatment testing of DPD deficiency; however, consider determination of DPD activity if drug toxicity is confirmed or suspected
- in cases of drug toxicity, consider stopping treatment with flucytosine
- report suspected adverse drug reactions associated with flucytosine on a Yellow Card

New recommendations following review

Flucytosine is an antifungal drug authorised to treat systemic yeast and fungal infections. It is typically used in combination with amphotericin to treat cryptococcal meningitis, severe systemic candidiasis, and other long-standing fungal infections. Flucytosine is a 5-fluorouracil prodrug, and systemic exposure of 5-fluorouracil has been observed in patients treated with flucytosine.

Following a European review of fluorouracil and related medicines, treatment with flucytosine is now contraindicated in patients with known complete DPD deficiency. A letter has been sent to healthcare professionals to inform of this new contraindication.

In order to avoid a delay in starting antimycotic therapy, testing for DPD deficiency is not required before treatment with flucytosine. However, determination of DPD activity should be considered when there is a confirmed or suspected drug toxicity. In case of suspected drug toxicity, consideration should be given to stopping treatment with flucytosine.

For recommendations for oncological medicines in which screening patients for DPD deficiency before treatment is recommended, see recommendation to identify patients at increased risk of severe and fatal toxicity.

About DPD deficiency

DPD activity is rate limiting in the catabolism of 5-fluorouracil. Patients with DPD deficiency who are treated with systemic 5-fluorouracil or its prodrugs are therefore at increased risk of

toxicity, including, for example, stomatitis, diarrhoea, mucosal inflammation, neutropenia, and neurotoxicity.

Patients with known complete DPD deficiency are at higher risk of developing life-threatening toxicity and must not be treated with flucytosine. In patients with partial DPD deficiency, the risk of severe drug toxicity is increased, with the level of toxicity correlating with the extent of DPD deficiency.

The majority of data on the frequency of DPD deficiency are in Caucasian people. The European review considered that complete DPD deficiency is rare (0.01–0.5% of Caucasian people). Partial DPD deficiency is estimated to affect 3–9% of Caucasian people.

Report on a Yellow Card

Please continue to report suspected adverse drug reactions (ADRs) on a Yellow Card. Reporting suspected ADRs, even those known to occur in association with the medicine, 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:

- on the Yellow Card website
- via the mobile app from the Google Play Store or Apple App Store
- some clinical IT systems for healthcare professionals (EMIS/SystmOne/Vision/MiDatabank)

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 3: October 2020: 2.

Niraparib (Zejula▼): reports of severe hypertension and posterior reversible encephalopathy syndrome (PRES), particularly in early treatment

Increase the frequency of blood pressure monitoring to at least weekly for the first 2 months, and then monitor monthly for the first year and periodically thereafter during treatment, following recent reports of onset of severe hypertension (including rare cases of hypertensive crisis) and rare cases of PRES within the first month of niraparib treatment.

Advice for healthcare professionals:

- there have been reports of severe hypertension (including rare cases of hypertensive crisis) with niraparib, including some with onset in the first month of treatment
- rare cases of posterior reversible encephalopathy syndrome (PRES) have also been reported, many associated with hypertension and within the first month of treatment
- before treatment, control pre-existing hypertension adequately before starting a patient on niraparib
- monitor blood pressure at least weekly for 2 months from initiation and then monthly afterwards for the first year and periodically thereafter during treatment
- consider home blood pressure monitoring for appropriate patients; provide adequate training and instruct them to contact their doctor in case of a rise in blood pressure
- during treatment, manage hypertension with antihypertensives and if necessary, consider treatment interruption and subsequent adjustment of the niraparib dose as advised in product information
- discontinue niraparib in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy
- in cases of PRES, discontinue niraparib and treat specific symptoms including hypertension
- report any suspected adverse drug reactions associated with niraparib to the Yellow Card scheme

Review of cases of severe hypertensive reactions and PRES

Niraparib (Zejula▼) is indicated as monotherapy for the maintenance treatment of adults with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

A recent European review of the safety data for niraparib identified worldwide reports of patients who developed severe hypertension, including rare cases of hypertensive crisis (may affect up to 1 in 1000 patients), as early as within the first month of treatment with niraparib.

The review also identified rare reports of PRES (may affect up to 1 in 1000 patients). Of 5 cases worldwide, 4 patients presented with severe hypertension and 3 reported that PRES occurred during the first month of therapy. Three reports originated from post-marketing sources and 2 from clinical trials.

Hypertension was identified as an important risk with niraparib in clinical trials. The product information for niraparib had an existing warning for hypertension, including hypertensive crisis, and recommended that blood pressure should be monitored monthly in the first year.

Based on the new information identified in the European review, safety warnings have been updated and hypertensive crisis and PRES both added into the product information as rare reactions. The product information has been amended to recommend more frequent blood pressure measurement, especially at the start of treatment.

For appropriate patients, home blood pressure monitoring can be considered with instruction for patients to contact their healthcare professional in case of rise in blood pressure. Adequate instructions should be provided to patients or caregivers on how to monitor blood pressure at home – consult NHS advice or local resources.

In the UK, up to 30 July 2020, the Yellow Card Scheme received 6 reports associated with hypertension for niraparib. However, limited information is available for the details of the hypertension, including time of onset. No UK Yellow Card reports have been received for PRES associated with niraparib.

Caution should be exercised in interpreting these data since there may be under-reporting and use of niraparib in the UK may be relatively low. Continued vigilance is recommended, and we ask for any suspected adverse drug reactions to be reported to the MHRA on a Yellow Card.

Characteristics of reactions

Hypertension, including hypertensive crisis, has been reported with the use of niraparib including in the first month of treatment.

PRES is a rare, reversible, neurological disorder. The presenting signs and symptoms of PRES include seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI).

The safety of reinitiating niraparib therapy in patients who have previously experienced PRES is not known.

Report on a Yellow Card

Niraparib (Zejula▼) is subject to additional monitoring and any suspected adverse drug reactions (ADR) should be reported to the Yellow Card Scheme.

Yellow Card reports can be made for suspected adverse drug reactions:

- on the Yellow Card website
- via the mobile app from the Google Play Store or Apple App Store
- through 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 3: October 2020: 3

Dolutegravir (Tivicay▼, Triumeq▼, Juluca▼): updated advice on increased risk of neural tube defects

Updated safety recommendations have been issued as part of the European review evaluating cases of neural tube defects in babies born to mothers who became pregnant while taking the HIV medicine dolutegravir.

Evidence collected as more women have given birth while on dolutegravir treatment shows a smaller increased risk than previously thought, almost comparable to other HIV drugs. The previous restrictions against use in pregnancy are no longer in place – inform women of the potential risk of neural tube defects with dolutegravir and discuss the benefits and risks of continuing treatment if a woman plans pregnancy.

Advice for healthcare professionals:

- counsel women of childbearing potential about the possible risk of neural tube defects with dolutegravir, including consideration of effective contraceptive measures
- discuss the benefits and the risks of continuing treatment with dolutegravir to women who are trying to become pregnant
- if a pregnancy is confirmed in the first trimester while a patient is on dolutegravir, the benefits and risks of continuing dolutegravir versus switching to another antiretroviral regimen should be discussed with the patient, taking into account the gestational age and the critical time period of neural tube defect development
- report any suspected adverse drug reactions associated with dolutegravir to the Yellow Card scheme

Risk of neural tube defects

In June 2018 preliminary results from an observational study suggested an increased risk of neural tube defects in infants born to women who took dolutegravir at the time of conception. While a review of this signal was ongoing, we issued a Drug Safety Update article asking healthcare professional not to prescribe dolutegravir to women who are trying to become pregnant. The product information for dolutegravir was amended with these recommendations and a letter was sent to healthcare professionals by the manufacturer.

The study is ongoing and since the article in 2018, additional women were included in the continuing analysis.

For a total of 19,361 babies born to women with HIV in Botswana, updated data showed 0.19% (95% CI 0.09–0.40) of babies (7 of 3,591) whose mothers became pregnant while taking dolutegravir had a neural tube defect, compared with 0.11% (0.07–0.17) of babies (21 of 19,361) whose mothers took other HIV medicines.

The latest review also investigated cases of birth defects in babies born to women who took dolutegravir during pregnancy reported from the Antiretroviral Pregnancy Registry with 660 women exposed to dolutegravir during pregnancy.

These data do not indicate an increased risk of major birth defects associated with dolutegravir treatment (absolute risk difference of neural tube defects between dolutegravir and other HIV treatment at conception of 0.08 [95% CI –0.03 to 0.30]). However, because of the rarity of the neural tube defects, these data are insufficient to completely rule out any risk. Changes will be made to product information advice to reflect the latest review of data.

The review of the study is ongoing. Further advice will be communicated as appropriate as important new information becomes available.

Background

▼Dolutegravir is an integrase inhibitor indicated in combination with other anti-retroviral medicinal products for the treatment of HIV in adults, adolescents, and children older than 6 years.

In the EU, dolutegravir has been authorised since 2014. It is marketed on its own as Tivicay and in combination with lamivudine and abacavir as Triumeq or in combination with rilpivirine hydrochloride as Juluca. Further information on these medicines can be found in the Summaries of Product Characteristics.

Report on a Yellow Card

Any suspected adverse drug reactions with dolutegravir (Tivicay▼, Triumeq▼, Juluca▼) should be reported without delay on a Yellow Card.

Yellow Card reports can be made for suspected adverse drug reactions:

- on the Yellow Card website
- via the mobile app from the Google Play Store or Apple App Store
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank and Ulysses

Please report to the Yellow Card Scheme suspected adverse reactions associated with medicines taken during pregnancy or breastfeeding experienced by women or the baby or child.

Any patients, caregivers, or healthcare professionals can report a Yellow Card when they suspect a medication used during pregnancy has caused an adverse reaction or abnormal pregnancy outcome.

Article citation: Drug Safety Update volume 14, issue 3: October 2020: 4.

Warfarin and other anticoagulants: monitoring of patients during the COVID-19 pandemic

Following concerns raised by clinicians during the coronavirus (COVID-19) pandemic, we have issued advice to healthcare professionals and patients regarding the safe use of warfarin and other anticoagulants. This advice has been endorsed by the Commission on Human Medicines (CHM).

Healthcare professionals are reminded that:

- acute illness may exaggerate the effect of warfarin and necessitate a dose reduction; patients on warfarin or other vitamin K antagonists should therefore be asked to tell their GP or healthcare team if they have symptoms of, or confirmed, COVID-19 infection

- continued INR (international normalised ratio) monitoring is important in patients taking warfarin or other vitamin K antagonists if they have suspected or confirmed COVID-19 infection, so they can be clinically managed at an early stage to reduce the risk of bleeding

- both vitamin K antagonists and direct-acting oral anticoagulants (DOACs) may interact with other medicines and if a patient using these oral anticoagulants is also prescribed antibiotics or antivirals, follow advice in the product information for minimisation of risk of potential interactions – this includes INR monitoring in patients taking vitamin K antagonists who have recently started new medicines

- if patients are switched from warfarin to a DOAC, warfarin treatment should be stopped before the DOACs is started to reduce the risk of over-anticoagulation and bleeding

- patients taking vitamin K antagonists should be reminded to carefully follow the instructions for use for anticoagulant medicines (including the patient information leaflet) and to tell their GP or healthcare team if they:
    - are otherwise unwell with sickness or diarrhoea or have lost their appetite
    - are taking any new medicines or supplements
    - have changed their diet, smoking habits, or alcohol consumption
    - are unable to attend their next scheduled blood test for any reason, including because they feel unwell.

Report on a Yellow Card

Suspected adverse drug reactions should be reported to the Yellow Card scheme. Any suspected adverse drug reactions associated with any medicine used in patients with confirmed or suspected COVID-19, including medicines to manage long-term or pre-existing conditions such as anticoagulant medicines, should be reported to the COVID-19 Yellow Card reporting site.

Article citation: Drug Safety Update volume 14, issue 3: October 2020: 5.

Every report counts: report suspected adverse drug reactions and take part in #MedSafetyWeek (2–8 November 2020)

Remain vigilant for suspected adverse drug reactions and report them to the Yellow Card scheme. Show your support during #MedSafetyWeek on 2–8 November 2020 by sharing material on social media and discussing with colleagues and patients the importance of reporting suspected adverse drug reactions.

What can healthcare professionals do to support MedSafetyWeek?

- don't delay in reporting suspected adverse drug reactions to the Yellow Card scheme online or via the Yellow Card app (download from the Apple App Store or Google Play Store)
- when prescribing, repeat prescribing, dispensing, administering or reviewing medicines, consider discussing the possible side effects with your patient – you could talk about:
    - reading the patient information leaflet that comes with their medicines – this lists possible side effects and advises them on what to do if they do experience these
    - the purpose of the Yellow Card scheme and how reporting any suspected problems can help the safe use of medicines for others
- use the product information for medicines to find information on interactions, relevant precautions, and safety monitoring advice; talk to your colleagues about the importance of following the product information advice on monitoring and being vigilant for new adverse reactions
- discuss with colleagues emerging news from Drug Safety Update and how reporting suspected adverse drug reactions to the Yellow Card scheme helps to improve the safe use of medicines
- encourage your colleagues to sign up to receive monthly alerts for Drug Safety Update and other safety information from the MHRA about medicines and medical devices – these messages are also available through the Yellow Card app
- follow the MHRA on its social media channels and show your support for the importance of reporting by retweeting, commenting, liking, and sharing material to help promote the campaign (see How to support #MedSafetyWeek on page 13)

This year's theme: 'Every report counts'

The theme of the campaign for 2020 is 'every report counts' and reporting helps others in future. The campaign will also mark receipt of its 1 millionth adverse drug reaction report since the Yellow Card scheme was established more than 50 years ago. The campaign calls upon patients, parents, and carers, as well as healthcare professionals and their organisations, to report suspected adverse drug reactions to medicines. We advise people not to wait for someone else but rather to report their suspicions directly as soon as they can.

During the coronavirus (COVID-19) pandemic, Yellow Card reporting of suspected adverse drug reactions has decreased, especially from healthcare professionals. We appreciate healthcare professionals are under pressure at this challenging time, but reporting remains essential to patient safety.

It is hard to predict who will experience an adverse drug reaction, but it is essential that any potential risks are understood and communicated to patients and healthcare professionals. Reporting helps to identify new adverse drug reactions, recognise unexpected and serious safety problems, and gain more information about known effects. By reporting, you can help the safe use of medicines for everyone since this helps the MHRA to protect the public's health through effective risk minimisation.

The Yellow Card scheme has identified many new safety issues that were unknown before being reported to the MHRA and this has enabled us to take action to minimise the risk to other patients. For example, one pharmacist used the Yellow Card Scheme to report a potential choking risk to patients – see Video online.

How to report

Yellow Cards can be used for reporting suspected adverse drug reactions to medicines, vaccines, herbal or complementary products, whether self-medicated or prescribed. The MHRA website provides full guidance on reporting a Yellow Card.

Yellow Card reports can be made for suspected adverse drug reactions:

- on the Yellow Card website
- via the mobile app from the Google Play Store or Apple App Store
- in some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank and Ulysses)

Reports can also be made via freephone (0800 731 6789, 9am to 5pm Monday to Friday).

Anyone can use the Yellow Card scheme to also report online any incidents involving medical devices (and via the app), defective, fake medical products and safety concerns for e-cigarettes or their refill containers (e-liquids). Please note, any medical device incidents should be reported to Health Facilities Scotland in Scotland and to the Northern Ireland Adverse Incident Centre in Northern Ireland.

Please use the Coronavirus Yellow Card reporting site to report suspected side effects to medicines or medical device and diagnostic adverse incidents used in coronavirus treatment. Please note that the reporting of incidents in clinical trials should follow trial protocols.

How to support #MedSafetyWeek

The annual MedSafetyWeek forms part an international effort to raise awareness about the importance of reporting suspected adverse drug reactions with national medicines regulatory authorities from 74 countries across the globe and their stakeholders participating. For more information see the Yellow Card Campaigns website.

We ask all healthcare professionals to show their support for the importance of reporting by retweeting, commenting, liking, and sharing material with their fellow colleagues and communication colleagues. Please help to promote the campaign by using #Everyreportcounts #MedSafetyWeek #patientsafety, #yellowcard.

Additional supporting information will be made available on the campaigns and resources tabs of the Yellow Card website during MedSafetyWeek. For example, use the email signature to help promote the campaign.

Article citation: Drug Safety Update volume 14, issue 3: October 2020: 6.

Letters and drug alerts sent to healthcare professionals in September 2020

Letters

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

- Sandostatin LAR (octreotide) 30mg powder and solvent for suspension for injection: Incorrect dosage information on one side of carton
- NULOJIX (belatacept): Extension of the temporary restriction in supply up until 4Q 2021 (initiated in March 2017)

We are also aware of the following letters issued or provided to healthcare professionals in October 2020:

- Nytol Liquid Caramel Flavour 10 mg/5 ml oral solution (diphenhydramine hydrochloride): removal of the allergy indication; should only be sold as an adult sleep aid
- ONIVYDE pegylated liposomal 4.3 mg/ml concentrate for dispersion for infusion (Irinotecan): interim supply of Irish stock to mitigate supply disruption
- Semglee▼ 100 units/ml x 3ml prefilled pens (Insulin glargine): interim supply of Portuguese stock to mitigate supply disruption

Drug alerts

Class 4 FMD Medicines Information: WDA(H) 49276 Kingsley Specials Ltd, Multiple Products, (EL (20)A/42). Issued 1 September 2020. The MHRA is currently investigating an incident where several medicines appear to have left the legal supply chain and have then been re-introduced via Kingsley Specials Ltd WDA(H) 49276, who purchased from a company that do not hold a wholesale dealers authorisation and then sold it on to a number of other wholesalers. Follow advice in the alert for identifying affected products.

Class 3 Medicines Recall: Accord Healthcare Limited, Amlodipine 10mg Tablets. Issued 7 September 2020. A specific batch of Amlodipine 10mg tablets is being recalled as a precautionary measure due to out of specification results obtained during stability testing. Stop supplying the batch immediately and return to supplier.

Class 4 Medicines Defect Information: Zopiclone Tablets, Ratiopharm UK Limited and Generics [UK] Limited t/a Mylan, EL (20)A/44. Issued 10 September 2020. The Patient Information Leaflet (PIL) within all packs and the Summary of Product Characteristics (SmPC) for Ratiopharm products is missing important safety information related to potential suicide risks. If dispensing, make patients aware of missing information from the PIL provided in their packs.

Class 2 FMD Medicines Recall, Parallel Distributed Medicines, Multiple Products, EL (20)A/45. Issued 16 September 2020. Medicines from the listed parallel distributors are being recalled due to concerns that the supply chain may have been compromised and the origins of the products are unknown. Follow the advice in the alert for return of affected batches.

Class 3 Medicines Recall: Theramex Ireland Ltd T/A Theramex HQ UK Ltd, AlfaD Capsules, EL (20) A/46. Issued 29 September 2020. When decommissioning at the pharmacy and when scanning the serialised 2D code, the status of certain packs of AlfaD capsules may report as 'EXPORT'. Although there is no risk to product quality, any remaining stock should be quarantined and returned.

Healthcare professionals should also be aware of the following alert, issued October 2020: Class 2 Medicines Recall: Sanofi Epilim 500mg Gastro-Resistant Tablets EL (20)A/48. Issued 14 October 2020. Batches of this valproate medicine are being recalled as a precautionary measure due to out of specification results during routine stability testing. Stop supplying the batch immediately and return to supplier.

Subscribe to email alerts from the MHRA, including to receive drug alerts and MHRA devices safety information. This includes the new Medical Devices Safety Bulletin – a regular bulletin to inform health and care professionals of new or ongoing safety issues with medical devices.

Article citation: Drug Safety Update volume 14, issue 3: October 2020: 7.