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 prescribers of CDK4/6 inhibitors that cases of interstitial lung disease and pneumonitis have been reported in patients receiving these medicines, indicated for some breast cancers (page 2). We ask healthcare professionals to ensure that patients taking these medicines are aware of the need to seek advice right away if they develop new or worsening respiratory symptoms.

Next, we inform of cases of severe cutaneous adverse reactions, including Stevens-Johnsons syndrome and toxic epidermal necrolysis, reported in patients treated with immune-stimulatory anti-cancer drugs, including atezolizumab (page 5). We ask healthcare professionals to advise patients being treated with these medicines to seek urgent assistance if they experience signs of severe skin reactions.

On page 8 we summarise recent advice relating to COVID-19 vaccines that has been published since the May 2021 issue of Drug Safety Update. And on page 9 we include recent letters, recalls and notifications sent to healthcare professionals about medicines and medical devices.

At the end of the issue, we also include a survey seeking the views of healthcare professionals working in a GP setting regarding a new MHRA initiative to establish a Yellow Card Biobank for researchers to investigate genetic factors behind adverse drug reactions and optimise the safe use of medicines and vaccines. See page 10 for a link to the survey.

CDK4/6 inhibitors (abemaciclib▼, palbociclib▼, ribociclib▼): reports of interstitial lung disease and pneumonitis, including severe cases

Cases of interstitial lung disease and pneumonitis have been reported in patients receiving CDK4/6 inhibitors indicated for some breast cancers. Ensure that patients taking these medicines are aware of the need to seek advice right away if they develop new or worsening respiratory symptoms.

Advice for healthcare professionals:

- abemaciclib, palbociclib, and ribociclib are indicated for some locally advanced or metastatic breast cancer (see product information for full indications)
- there have been reports of interstitial lung disease and pneumonitis with these medicines, in some cases severe or fatal
- during clinic appointments, ask patients about pulmonary symptoms indicative of interstitial lung disease and pneumonitis, such as cough or dyspnoea, and advise them to seek advice right away if they occur
- evaluate patients with new or worsening respiratory symptoms, refer to the Summary of Product Characteristics (SmPC; linked above) particularly advice in sections 4.2 and 4.4 and consider dose interruption, modification, or discontinuation according to the severity of the event
- ensure patients are provided with a copy of the Patient Information Leaflet (PIL), which provides information about the medicine and explains the symptoms that patients should be aware of
- report all suspected adverse drug reactions associated with CDK4/6 inhibitors to the Yellow Card scheme

Advice for healthcare professionals to provide to patients:

- if you are experiencing new or worsening respiratory symptoms such as a cough or shortness of breath when taking a CDK4/6 inhibitor, it is important to seek advice right away from your care team
- cases of lung disease, including inflammation in the lungs, have been reported in patients taking these medicines; these lung conditions can be severe or life-threatening
- always read the leaflet that accompanies your medicines and talk to your doctor, nurse, or pharmacist if you are concerned about any side effects

CDK4/6 inhibitors

Cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6 inhibitors) abemaciclib (Verzenios▼), palbociclib (Ibrance▼), and ribociclib (Kisqali▼) are authorised for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant – see product information for full indication for each medicine.

In premenopausal or perimenopausal women, the endocrine therapy should be combined with a luteinising-hormone-releasing hormone (LHRH) agonist (see product information for full details).

Review of cases of interstitial lung disease and pneumonitis

Cases of interstitial lung disease and pneumonitis have been reported with the use of CDK4/6 inhibitors abemaciclib, palbociclib, and ribociclib. There have also been reports of some fatal cases.

Following European reviews of safety data, the Summary of Product Characteristics (SmPC) and Patient Information Leaflets (PILs) for these products have been updated to include warnings about these risks. In patients who have new or worsening respiratory symptoms and who are suspected to have developed interstitial lung disease or pneumonitis, refer to the product information, particularly advice in sections 4.2 and 4.4 of the SmPC, and consider dose interruption, modification, or discontinuation according to the severity of the event.

Frequency of interstitial lung disease and pneumonitis

Clinical trials

For abemaciclib, the product information notes that 3.4% of participants treated in clinical trials (n=768) had interstitial lung disease or pneumonitis of any grades of severity. The frequency of grade 3 (severe) events was 0.4% and grade 4 (life-threatening) events was 0.1% of participants.[1]

For palbociclib, the product information notes that 1.4% of participants treated in clinical trials (n=872) had interstitial lung disease or pneumonitis of any grade. One grade 3 event was reported (0.1%) and no grade 4 events (although fatalities have been reported post-marketing).

For ribociclib, the product information notes that interstitial lung disease (any grade 0.3%, including 0.1% grade 3) was reported in the ribociclib-treated group in clinical studies, with no cases in the placebo-treated group. Pneumonitis was reported in both the ribociclib and the placebo-treated groups (any grade 0.4%; with no grade 3 or 4 events in either group).

Yellow Card reports in the UK

CDK4/6 inhibitors are relatively new medicines. Palbociclib, ribociclib, and abemaciclib were licensed in the EU in 2016, 2017, and 2018 respectively. Since authorisation and up to 21 Jan 2021, the number of suspected adverse reports of interstitial lung disease, pneumonitis and related terms in the UK received by the Yellow Card scheme was 8 for abemaciclib (of which 4 were fatal), 18 for palbociclib (of which 7 were fatal), and one for ribociclib.

In interpreting these data, caution should be exercised and comparisons not drawn between the medicines given different exposures[2] and other factors unrelated to the inherent safety of the medicines that may affect the number of reports. Reporters are asked to submit Yellow Card reports even if they only have a suspicion that the medicine may have caused the adverse drug reaction.

Report any suspected adverse drug reactions

Please continue to report suspected adverse drug reactions (ADRs) via the Yellow Card scheme. All ADRs associated with black triangle medicines should be reported – this will allow quick identification of new safety information.

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 or medical device and diagnostic adverse incidents used in coronavirus (COVID-19) using the dedicated Coronavirus Yellow Card reporting site or the Yellow Card app. See the MHRA website for the latest information on medicines and vaccines for COVID-19.

Article citation: Drug Safety Update volume 14, issue 11: June 2021: 1.

Footnotes

1. Grading of events according to Common Terminology Criteria for Adverse Events (CTCAE). Consult SmPC for relevant information on version used.

2. Estimated usage for these medicines in the UK is 940 patient-years for abemaciclib, 7850 patient-years for palbociclib, and 780 patient-years for ribociclib (data derived from IQVIA MIDAS, quarter 4 2016, to quarter 3 2020, by the MHRA, February 2021). Data based on volume of drug dispensed in UK retail and hospital pharmacies. Patient-year estimates made using defined daily dose.

Atezolizumab (Tecentriq▼) and other immune-stimulatory anti-cancer drugs: risk of severe cutaneous adverse reactions (SCARs)

Cases of severe cutaneous adverse reactions, including Stevens-Johnsons syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients treated with immune-stimulatory anti-cancer drugs, including atezolizumab. Advise patients to be vigilant for the signs of severe skin reactions and to seek urgent medical advice if they occur.

Advice for healthcare professionals:

- severe cutaneous adverse reactions (SCARs), including cases of Stevens-Johnsons syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients treated with immune-stimulatory anti-cancer drugs including atezolizumab
- advise patients of the need to seek urgent medical assistance if severe skin reactions occur
- monitor patients for signs and symptoms of severe skin reactions and exclude other causes
- if a SCAR is suspected, treatment should be withheld, and patients referred to a specialist for diagnosis and treatment
- if SJS or TEN is confirmed, or for any grade 4 (life-threatening) SCAR, permanently discontinue treatment with the immune-stimulatory drug
- caution is recommended when considering the use of immune-stimulatory drugs associated with SCARs in patients with previous history of life-threatening SCAR with other immune-stimulatory anti-cancer drugs
- report suspected adverse drug reactions on a Yellow Card – all suspected adverse drug reactions to black triangle medicines should be reported

Advice for healthcare professionals to provide to patients:

- contact your doctor straight away if you experience itching, skin blistering, peeling or sores, or ulcers in the mouth or in lining of nose, throat or genital area
- always read the leaflet that accompanies your medicines and talk to your doctor, nurse, or pharmacist if you are concerned about any side effects

Review of atezolizumab and SCARs

Atezolizumab (Tecentriq▼) is an immune-stimulatory drug indicated for cancers including those of the bladder, lung, and liver – see product information for full indications.

Severe cutaneous adverse reactions (SCARs) were previously known to be potentially associated with the use of atezolizumab. Based on evidence from a recent analysis (see detailed cases in next section), SCARs are now considered to be an identified risk for atezolizumab.

The product information, including the Patient Information Leaflet, has been updated to include information about these reactions and a letter sent to prescribers of this medicine.

Although review of the cases worldwide found no reports of SCARs for patients on atezolizumab with a history of these reactions with another immune-stimulatory drug, healthcare professionals are advised to carefully consider the use of atezolizumab in patients who have had a severe or life-threatening SCAR following treatment with an immune-stimulatory anti-cancer drug.

Details of cases reported with atezolizumab

A review of safety data for atezolizumab and risk of SCARs was recently completed in Europe. As of 31 July 2020, a cumulative analysis of the company's safety database identified 99 cases of SCARs worldwide (97 of which were serious). Of the 99 cases, the majority (48%) were reported from clinical studies, with 30% from post-marketing settings. Approximately 23,654 clinical trial patients and 106,316 patients in post-marketing settings worldwide have been exposed to atezolizumab as of 17 May 2020.[1]

1 Exposure data used with agreement of Roche, 2021.

Of the 99 cases, 35 cases were identified as erythema multiforme, 25 cases as Stevens-Johnsons syndrome (SJS), 12 cases as a toxic skin eruption, 8 cases as toxic epidermal necrolysis (TEN), 7 cases as dermatitis bullous, 6 cases as dermatitis exfoliative generalised, 4 cases as drug reaction with eosinophilia and systemic symptoms (DRESS), and 2 cases as skin necrosis.

Of the 99 cases of SCARs, 36 were confirmed by histopathology or specialist diagnosis. Of which, 5 cases were considered to be of likely causality and 20 cases were possibly temporally related to multiple suspect medications including atezolizumab.

In the majority of cases (55 of 99), the outcome was reported as recovered, in 21 cases the patients were recovering, and in 14 cases the patients had not recovered. One elderly patient who received atezolizumab monotherapy died.

Based on clinical trials and post-marketing data, the most frequently reported range of time to onset was within 1 month after the first dose of atezolizumab (37%; 38 cases). Where reported, atezolizumab treatment was withdrawn or interrupted in 58 cases and the dose was not changed in 16 cases.

The incidence rates of SCARs, regardless of severity, from pooled atezolizumab monotherapy (n=3178) and combination therapy (n=4371) company-sponsored clinical studies was 0.7% and 0.6% respectively.

Risk of SCARs with other immune-stimulatory drugs

Other products used for cancers in the same class as atezolizumab, including cemiplimab, ipilimumab, nivolumab, and pembrolizumab list SCARs (including SJS and TEN) as a possible side effects in the Summary of Product Characteristics (SmPC) with an associated warning and precautions. Avelumab and durvalumab are known to cause other immune-mediated skin adverse reactions. As for the other immune-stimulatory anti-cancer drugs, patients should be monitored for the signs and symptoms of serious skin reactions and treatment withheld or discontinued according to the severity of the event as described in the SmPC for each product.

Since authorisation and up to 13 June 2021, in the UK, Yellow Cards reporting SJS, TEN or DRESS have been received for atezolizumab (n=2), ipilimumab (n=13), nivolumab (n=15), and pembrolizumab (n=9). In interpreting these data, caution should be exercised and comparisons not drawn between the medicines given different exposures and other factors unrelated to the inherent safety of the medicines that may affect the number of reports. Reporters are asked to submit Yellow Card reports even if they only have a suspicion that the medicine may have caused the adverse drug reaction.

About severe cutaneous adverse reactions (SCARs)

SCARs are a heterogeneous group of delayed hypersensitivity reactions. These events mainly consist of acute generalised exanthematous pustulosis (AGEP), SJS, TEN, and DRESS and can be potentially life-threatening, and lead to severe, potentially chronic, sequelae.

Immune-stimulatory anti-cancer drugs

Immune-stimulatory anti-cancer drugs authorised in the UK include: Tecentriq▼ (atezolizumab), Bavencio▼ (avelumab), Libtayo▼ (cemiplimab), Imfinzi ▼ (durvalumab), Yervoy (ipilimumab), Opdivo (nivolumab), and Keytruda (pembrolizumab). These medicines are used as monotherapy or combination therapy with other immune-stimulatory drugs or chemotherapeutic drugs and are indicated for a variety of cancers.

Report suspected reactions on a Yellow Card

Please continue to report suspected adverse drug reactions (ADRs via the Yellow Card website or Yellow Card app (Apple App Store or Google Play Store). All ADRs associated with black triangle medicines should be reported – this will allow quick identification of new safety information.

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.

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COVID-19 vaccines: updates for June 2021

Here we include a summary of key MHRA advice issued up to 11 June 2021 and since the publication of the May 2021 edition of Drug Safety Update.

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 will be published regularly to include other safety investigations carried out by the MHRA under the COVID-19 Vaccine Surveillance Strategy.

Information about our review of reports of menstrual disorders and unexpected vaginal bleeding with the three COVID-19 vaccines currently being used in the UK has been included in the weekly summary. The current evidence does not suggest an increased risk of either menstrual disorders or unexpected vaginal bleeding following vaccination with the vaccines reviewed (Pfizer/BioNTech, COVID-19 Vaccine AstraZeneca or COVID-19 Vaccine Moderna). Our advice remains that the benefits of the vaccine outweigh the risks for most people. We will continue to closely monitor reports of suspected menstrual disorders and vaginal bleeding with COVID-19 vaccines.

We take every report of a suspected adverse reaction seriously and encourage everyone to report through the Coronavirus Yellow Card reporting site.

We have also recently:

- authorised an extension to the current UK approval of the Pfizer/BioNTech COVID-19 vaccine that allows its use in 12 to 15 year-olds
- given regulatory approval to the COVID-19 vaccine developed by Janssen after it met the required safety, quality and effectiveness standards

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

We previously included a summary of latest advice in the January 2021, February 2021, March 2021, April 2021 and May 2021 issues of Drug Safety Update.

Article citation: Drug Safety Update volume 14, issue 11: June 2021: 3.

Letters and medicine recalls sent to healthcare professionals in May 2021

Letters

In May 2021, the following letters were sent or provided to relevant healthcare professionals:

- INOmax (nitric oxide): Difficulties in closing the cylinder valves after use if the cylinder is not empty: precautions for use when disconnecting the cylinders from pressure regulators.

Medicine Recalls and Notifications

For all of the latest safety notices from the MHRA, see Alerts and recalls for drugs and medical devices, including a National Patient Safety Alert and Class 1 patient-level recall for a batch of Zentiva co-codamol 30/500 effervescent tablets (issued 16 June 2021).

In May 2021, recalls and notifications for medicines were issued on:

Class 4 Medicines Defect Information, Syonell 250mg Gastro-Resistant Tablets,(PL 35507/0191), Syonell 500mg Gastro-Resistant Tablets, (PL 35507/0192), EL (21)A/11. Issued 04 May 2021. The outer packaging of several batches of Syonell (valproate semisodium) 250mg and 500mg Gastro-resistant tablets were printed with an incorrect amount of the active ingredient valproate semisodium. There is no risk to product quality as a result of this issue, however, healthcare professionals are advised to exercise caution when dispensing the product.

Class 2 Medicines Recall: AstraZeneca UK Limited, Bricanyl Injection, 0.5 mg/ml solution for injection or infusion (PL 17901/0112), EL (21)A/12. Issued 17 May 2021. A batch of Bricanyl (terbutaline sulfate) 0.5mg/ml solution for injection or infusion is being recalled as a precautionary measure due to irregular results for impurities identified during stability testing. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

Company led medicines recall: LysaKare 25 g / 25 g solution for infusion (PLGB 35145/0005). Issued 19 May 2021. A batch of LysaKare 25g/25g solution for infusion is being recalled due to the identification of leakages in a small number of bags. Quarantine all remaining stock and return to supplier once the manufacturer has supplied replacement products.

Class 3 Medicines Recall: Advanz Pharma, Carbimazole 10mg and 15mg tablets, EL (21)A/13. Issued 20 May 2021. Batches of Carbimazole 10mg and 15mg tablets are being recalled as a precautionary measure due to irregularities in the tablet appearance as a result of oxidation of the excipient red iron oxide on the tablet surface. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

Medical Device Safety Information

Recent MHRA Device Safety Information pages have been published on:

- Recall of BD Venflon Pro safety and Venflon Pro IV cannula

There was also a recent manufacturer's notice on:

- Recall of Certain Lots of Bausch + Lomb Contact Lens Solutions, Eye Wash and Eye Lubricants

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

Yellow Card Biobank GP survey

Finally, if you work in a GP setting, please complete this 5 to 10-minute survey to tell us your views on a new MHRA initiative to establish a Yellow Card Biobank for researchers to investigate genetic factors behind adverse drug reactions and optimise the safe use of medicines and vaccines.

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