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 11 Issue 12 July 2018

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, act on new advice on page 2 to avoid use of darunavir boosted with cobicistat (darunavir/cobicistat) in women who are pregnant. These recommendations follow new pharmacokinetic data suggesting low exposure to darunavir in the second and third trimester of pregnancy, which could lead to a risk of treatment failure and, potentially, maternal-to-child transmission of HIV-1. Darunavir/cobicistat should not be started in women who are pregnant and pregnant women who are already taking this combination should be switched to an alternative regimen, for example darunavir boosted with ritonavir.

Second, remind patients always to check the mouthpiece of their inhalers for loose objects before taking a dose and to replace the mouthpiece cover securely before storage (page 3). We have received reports of serious injuries, including airway obstruction, due to foreign object aspiration during inhaler use.

See page 5 for advice on testing of patients on eltrombopag, indicated for platelet disorders. Reports have been received of interference with creatinine and bilirubin testing results. If laboratory results are inconsistent with clinical observations, request re-testing with another method.

On page 7, you are reminded that medication error due to confusion between lipid-based and non-lipid-based formulations of parenteral amphotericin B can lead to risk of fatal overdose and that prescribers, pharmacists, and nurses need to be fully aware of the formulation being used and the associated dose regimen.

Finally, on page 8, we ask you always to report suspected adverse drug reactions for medicines taken during pregnancy to the Yellow Card Scheme. Detailed reports are essential to improved understanding of a medicine's effect during pregnancy and to ensure that healthcare professionals have up-to-date information on risks.

drugsafetyupdate@mhra.gov.uk

Darunavir boosted with cobicistat: avoid use in pregnancy due to risk of treatment failure and maternal-to-child transmission of HIV-1

New pharmacokinetic data show mean exposure of darunavir (brand name Prezista) boosted with cobicistat (available in combination in Rezolsta▼, Symtuza▼) to be lower during the second and third trimesters of pregnancy than during 6–12 weeks postpartum. Low darunavir exposure may be associated with an increased risk of treatment failure and an increased risk of HIV-1 transmission to the unborn child.

Advice for healthcare professionals:

- pharmacokinetic data show low exposure values of darunavir boosted with cobicistat (darunavir/cobicistat) during the second and third trimesters of pregnancy
- low darunavir exposure may be associated with an increased risk of treatment failure and an increased risk of mother-to-child transmission of HIV infection
- therapy with darunavir/cobicistat should not be initiated during pregnancy
- switch women who are pregnant and taking darunavir/cobicistat to an alternative regimen: darunavir/ritonavir may be considered as an alternative
- report suspected adverse drug reactions with HIV medicines to the Yellow Card Scheme, including treatment failure that results in harm

Background

Darunavir (Prezista) is an antiretroviral medication used to treat and prevent HIV/AIDS. Cobicistat can be co-administered with darunavir as a booster to increase darunavir levels. Darunavir and cobicistat are available in combination in fixed dose products Rezolsta▼ and Symtuza▼.

Data for lower exposure in pregnancy

New pharmacokinetic data based on 6 women enrolled in a Phase 3b study (TMC114HIV3015) showed lower mean exposure (AUC) levels of darunavir boosted with cobicistat (darunavir/cobicistat) during the second trimester (56% lower) and third trimester (50% lower) of pregnancy, compared with 6–12 weeks postpartum. Mean darunavir C_{min} concentrations were around 90% lower during the second and third trimesters of pregnancy than during 6–12 weeks postpartum. Exposure of cobicistat was 63% lower during the second trimester and 49% lower during the third trimesters of pregnancy than during 6–12 weeks postpartum.

Low darunavir exposure may be associated with an increased risk of treatment failure and an increased risk of HIV-1 transmission to the child. Mother-to-child transmission did not occur in any of the 6 infants born to the 6 mothers who delivered during study and completed the study. So far, the advice is precautionary, and we are not aware of any clinical pattern to suggest that patient safety has been affected.

Updates to product information

The product information for Prezista (darunavir), Rezolsta▼ (darunavir and cobicistat) and Symtuza▼ (darunavir, cobicistat, emtricitabine, tenofovir alafenamide) will be updated to recommend against use of darunavir/cobicistat in pregnancy. A letter has been sent to relevant healthcare professionals to inform them of this information.

Report suspected adverse drug reactions with HIV medicines

Report any suspected adverse drug reactions with black triangle drugs such as Rezolsta▼ and Symtuza▼ on a Yellow Card. Any cases of material-to-child transmission of HIV due to low treatment efficacy should be reported on a Yellow Card.

Article citation: Drug Safety Update volume 11, issue 12; July 2018: 1.

Pressurised metered dose inhalers (pMDI): risk of airway obstruction from aspiration of loose objects

Remind patients to check and remove the mouthpiece cover properly before inhaling a dose and to shake the inhaler to remove loose objects that may have become trapped in the inhaler during storage. The mouthpiece cover should be replaced securely after use. We have received reports of patients who have inhaled objects into the back of the throat, resulting in coughing. In some cases, objects were aspirated, causing airway obstruction.

Advice for healthcare professionals:

- train patients in the correct use of their inhaler; instructions for patients are provided in the patient information leaflet
- tell patients to remove the mouthpiece cover fully, shake the inhaler to remove loose objects that may not be visible, and check the inside and outside of the mouthpiece are clear before inhaling a dose
- to prevent objects entering the mouthpiece during storage, remind patients to replace the cover immediately after use, ensuring it clicks into place
- pharmacists dispensing a pMDI should emphasise to patients the need to clean the device regularly by following the instructions in the patient leaflet and to inspect the device for signs of damage; devices that are damaged should be replaced immediately
- please continue to report adverse incidents during use of inhalers, as well as suspected adverse reactions to the medicine, on a Yellow Card

Background

Pressurised metered dose inhalers (pMDI) are widely used for delivery of rescue and maintenance bronchodilator and anti-inflammatory therapies for asthma. The mouthpiece of the inhaler is protected by a removable plastic cover.

To avoid accidental inhalation of the mouthpiece cover, the patient must fully remove the cover before inhaling a dose. If the inhaler is stored without the cover, loose objects can become trapped within the mouthpiece and inhaled into the back of the throat, resulting in coughing. In some cases, objects were aspirated, causing airway obstruction.

Reports of accidental inhalation

Since 1987, we have received 22 reports from Yellow Cards and other sources of accidental inhalation of the mouthpiece cover or objects that have become trapped in the inhaler after dispensing when stored by patients. Additionally, we are aware of 36 cases reported outside of the UK.

Loose/foreign objects reported in these cases include tissues, stickers, coins, and plastic items. Some incidents resulted in pharyngeal injury, temporary asphyxiation, or surgical removal of aspirated objects. One patient experienced a pneumothorax.

Recently, we have received a report in which a foreign body was aspirated; it became lodged in the bronchus causing granulation and had to be removed bronchoscopically.

It is estimated that 5.4 million people are being treated for asthma in the UK.[1] Serious injuries from loose objects in inhalers are reported rarely. However, patients should be reminded to use caution.

1. Asthma UK. Asthma facts and statistics. Accessed July 2018.

It is essential that patients know to:

- remove the mouthpiece cover completely
- shake the device and check both the outside and inside of the mouthpiece is clear and undamaged before inhaling a dose
- store the inhaler with the mouthpiece cover on

Call for reporting

Please continue to report adverse incidents during use of the inhaler, as well as suspected adverse reactions to the medicine, on a Yellow Card.

Medication incidents where no harm has occurred should continue to be reported via local risk management systems.

Article citation: Drug Safety Update volume 11, issue 12; July 2018: 2.

Eltrombopag (Revolade): reports of interference with bilirubin and creatinine test results

If bilirubin and/or creatinine test results are inconsistent with clinical observations, request re-testing using another method to determine the validity of the result.

Advice for healthcare professionals:

- eltrombopag is highly coloured (reddish-brown) and can cause serum discolouration and interference with the test results of creatinine and bilirubin
- be aware that interference with bilirubin (falsely low/normal results) and creatinine (falsely high/normal results) may occur in patients taking eltrombopag
- if bilirubin and/or creatinine laboratory results are inconsistent with clinical observations, request re-testing using another method to determine the validity of the result
- the laboratory may consider susceptibility to serum discolouration and other factors that may be relevant when selecting an alternative test method
- report suspected adverse drug reactions, including any harm that occurs from a medicine interfering with laboratory test results, to the Yellow Card Scheme

Background

Eltrombopag is a small-molecule thrombopoietin receptor (TPO-R) agonist indicated for:

- chronic idiopathic thrombocytopenia (cITP) in patients who are refractory to other treatments
- thrombocytopenia in patients with chronic hepatitis C virus (HCV) infection
- the treatment of cytopenias in patients with severe aplastic anaemia who have had an insufficient response to immunosuppressive therapy

Due to a risk of abnormal liver function and severe hepatotoxicity with eltrombopag, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin should be measured before initiation, every 2 weeks during the dose-adjustment phase, and monthly following establishment of a stable dose. See Summary of Product Characteristics for more information, including recommendations for stopping treatment in cases of ALT elevations.

Reports of interference with bilirubin and creatinine test values

An EU review of data considered the available evidence of laboratory test interference (ie, bilirubin and creatinine) associated with eltrombopag. Up to 30 September 2017, the licence holder of Revolade received 9 reports worldwide of serum discolouration and interference with bilirubin and creatinine test values.

Six reports were of suspected interactions with bilirubin test values, of which 2 reported falsely low/normal bilirubin values (false-negative) despite clinically noticeable jaundice. Daily doses of eltrombopag were reported to be 75 mg in 4 cases, 150 mg in 1 case, and 300 mg in 1 case.

Three reports were of suspected interactions with creatinine test values leading to falsely high/normal values (false-positive). All 3 cases of a positive interaction with serum creatinine values were in patients with paediatric severe aplastic anaemia on high doses of eltrombopag (to 5 mg/kg and 7.5 mg/kg per day; equivalent to 375 mg).

Of the 9 reported cases of interference, 2 resulted in eltrombopag dose reductions and 2 led to temporarily discontinuation of the medicine. In 1 case eltrombopag was discontinued 4 days after suspected interference with a biological test due to lack of response. Two cases did not result in eltrombopag dose reductions and the action taken with eltrombopag was not reported in the remaining 2 cases.

In addition, several publications[1,2,3,4] describe potential negative interference from eltrombopag on bilirubin testing and positive interference on creatinine test values. Two publications[2,4] report that eltrombopag did not interfere with aminotransferases and blood urea testing findings.

Mechanism and clinical consequences

The mechanism for the eltrombopag interference with bilirubin and creatinine test values appears to be pH-dependent and method- or reagent-specific and related to the colour of eltrombopag in serum.

The false-positive interference with creatinine may result in a misleading clinical picture of apparent renal deterioration.

The interference with bilirubin is less likely to have clinically significant consequences since the stopping criteria for hepatic disorders are based on rises in ALT levels and clinical symptoms/evidence of hepatic decompensation, rather than bilirubin values alone.

Call for reporting

Please continue to report suspected adverse drug reactions to eltrombopag on a Yellow Card.

Article citation: Drug Safety Update volume 11, issue 12; July 2018: 3.

1. Cardamone D, et al. Eltrombopag and serum of a different hue. *Arch Pathol Lab Med* 2013; 137: 1175.

2. Choy K, et al. Eltrombopag: liver toxicity, kidney injury or assay interference? *Pathology* 2016; 48: 754–56.

3. Fontan Abad A, et al. Brownish plasma colour, associated with eltrombopag administration. 22nd IFCC-EFLM, 25th Meeting of the Balkan Clinical Laboratory Federation. June 11–15, 2017. 55; pp S732.

4. Gouden V, Zhao Z. Eltrombopag interference in routine chemistry testing. Ann Clin Biochem 2015; 53: 611–14.

Parenteral amphotericin B: reminder of risk of potentially fatal adverse reaction if formulations confused

Following receipt of a third case of fatal medication error caused by the administration of Fungizone (a non-lipid-based formulation of amphotericin B) instead of a lipid-based formulation (AmBisome, Abelcet), we remind healthcare professionals that these formulations are not interchangeable. Prescribers, pharmacists, and nurses need to be fully aware of the formulation being used and the associated dose regimen.

Advice for healthcare professionals:

- when prescribing, communicating and dispensing amphotericin products, use both the complete generic name and the proprietary name:
    - non-lipid amphotericin (Fungizone)
    - liposomal amphotericin (AmBisome)
    - lipid-complex amphotericin (Abelcet)
- verify the product name and dose before administration, especially if the dose prescribed exceeds 1·5 mg/kg—the maximum recommended dose for Fungizone.
- report suspected adverse reactions associated with amphotericin B, including medication error with associated harm to patients, on a Yellow Card
- report medication errors or near misses without harm to patients via local risk management systems that feed into the National Reporting and Learning System

Background

Parenteral amphotericin B is available as lipid-based (AmBisome, Abelcet) and non-lipid-based (Fungizone) formulations for the treatment of severe fungal infections. These different formulations of amphotericin B have different dose requirements. The appropriate dose and method of administration differ markedly between the marketed parenteral formulations of amphotericin B and they are therefore not interchangeable.

Amphotericin B overdoses may result in potentially fatal cardiac or cardiorespiratory arrest. The total daily dose of Fungizone should not exceed 1·5 mg/kg.

Fatal cases due to confusion

We are currently aware of three fatal overdoses which were caused by medication error in which Fungizone was administered (a non-lipid-based formulation of amphotericin B) instead of a lipid-based formulation.

Particular care must be taken in prescribing and dispensing the correct parenteral formulation of amphotericin B: prescribers, pharmacists, and nurses need to be fully aware of the formulation being used and the associated dose regimen.

Following earlier cases of medication error (see Drug Safety Update, March 2010), cautionary statements are present on Fungizone packages, cartons, and vial labels.

Latest MHRA review

We are currently reviewing available data to determine whether further measures are required to minimise the risk to patients. Further advice will be communicated as appropriate when the review is complete.

Further information

NPSA Alert. Non-lipid and lipid formulations of injectable amphotericin. 2007.

Article citation: Drug Safety Update volume 11, issue 12; July 2018: 4.

Medicines taken during pregnancy: please report suspected adverse drug reactions, including in the baby or child, on a Yellow Card

Report to the Yellow Card Scheme suspected adverse reactions associated with medicines taken during pregnancy experienced by women or the baby or child. Obstetricians and midwives have a particularly important role in providing data about pregnancy outcomes – your reports are essential to improving understanding of the safety of medicines for women and children.

Medicines in pregnancy

Medicines should not be taken in pregnancy unless absolutely necessary. However, some women with serious illnesses will need to take medicines to protect their health and that of the baby.

We are concerned that under-reporting in this important area may lead to missing drug safety signals, including miscarriage, congenital anomalies, or developmental disorders.

We welcome reports from those in the field of obstetrics such as obstetricians and midwives, who are able to provide key information such as results from prenatal scans and background information surrounding a pregnancy, which greatly contribute to post-marketing safety assessment of medicines.

Why is it important to report effects from use of medicines in pregnancy?

The Yellow Card Scheme is the UK system for monitoring the safety of medicines and healthcare products to ensure that they are acceptably safe for use by patients.

When a medicine is licensed, there is often limited information on effects from use in pregnancy. Therefore, information about medicines used during pregnancy and any suspected adverse drug reactions in the mother or child is essential to improve our understanding of a medicine's effect during pregnancy and ensure that healthcare professionals have up-to-date information on risks.

Reporting is the most common source of post-licensing data available on the safety of medicines used during pregnancy, and the most common evidence base for taking restrictive regulatory action.

Any patients, caregivers, or healthcare professionals, including midwives and obstetricians, can report a Yellow Card when they suspect a medication used during pregnancy has caused an adverse reaction or abnormal pregnancy outcome. Reports should also be made when an adverse effect associated with a medicine is suspected in a pregnancy that was not carried to term.

What to report?

For cases concerning exposure during pregnancy, the reporter will be asked to tick a checkbox if the patient is pregnant. It is important to provide as much information as possible in relation to the suspected adverse reaction in the mother or child.

We also encourage you to include the following, where available:

- Last menstrual period and expected date of delivery if the pregnancy is ongoing and dates when the medicine was taken
- Other medicines and/or vaccines taken during pregnancy (including folic acid, herbal medicines and/or any medicine obtained without a prescription), with dates
- Whether the mother has had her 20-week scan yet
- Details of any maternal medical history/current maternal medical condition relevant to this pregnancy (this can include details such as IVF conception and antenatal scans, any other significant events during the pregnancy)
- Any complications at delivery (such as emergency caesarian section, fetal distress, or complications in the baby)
- Details of any previous pregnancies and outcomes

Some suspected adverse reactions due to exposure during pregnancy may not be noticeable until later in the child's life. These types of reports are also extremely important to submit.

How to report?

You can report Yellow Cards for all medicines, on the Yellow Card website.

You can also report suspected adverse reactions to medicines:

- via the free Yellow Card app; download now from the Apple App Store or Google Play Store
- through some clinical IT systems (SystmOne/Vision/MiDatabank)
- by phone: 0800 731 6789 (freephone number, 10am to 2pm Monday-Friday)
- using forms in the BNF, MIMS, or PAGB OTC directory
- by downloading forms from the Yellow Card website and sending them freepost to 'Yellow Card'

MHRA may request more detailed information and follow-up about the outcomes of the pregnancy as necessary. Therefore, when reporting, please provide sufficient contact information to allow for this.

More information for healthcare professionals can be found on the MHRA website.
If in doubt as to whether to report a suspected adverse drug reaction, please complete a Yellow Card. Please do not assume someone else has reported it. Your Yellow Card report makes a difference to improving patient safety.

Article citation: Drug Safety Update volume 11, issue 12; July 2018: 5.

Letters sent to healthcare professionals in June 2018

In June 2018, letters were sent to healthcare professionals about:

- Cetrotide (cetrorelix acetate): Risk of missed doses or loss of sterility when using new syringe with different design
- Eperzan▼(albiglutide): reminder letter regarding the discontinuation
- Darunavir/cobicistat: Increased risk of treatment failure and increased risk of mother-to-child transmission of HIV infection when darunavir and cobicistat coadministered, due to low exposure values during the second and third trimesters of pregnancy
- Keytruda▼ (pembrolizumab): Restriction of indication for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy
- Denzapine 50 mg/mL Oral Suspension (clozapine): risk of loss of efficacy due to crystallisation of the suspension; always follow instructions for use, including 24 hours before first dosing, see company-led recall
- Bleo-Kyowa (bleomycin sulphate), powder for solution for injection: use 5-micron filter during IV infusion or pre-injection, see class 4 medicines defect information

Please continue to submit your thoughts on how we can improve the communication of medicines safety issues to support safe and effective use. Complete this 10-minute survey today.

Article citation: Drug Safety Update volume 11, issue 12; July 2018: 6.

Medical Device Alerts issued in June 2018

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:

- Smiths Medical CADD Non Flow-Stop Medication Cassette Reservoirs – recall of specific lots due to risk of under delivery of medication
- Alaris Smartsite Add-On Bag Access device – removal and destruction of specific batches due to risk of disconnection or leakage
- Combur10 Test UX and Chemstrip 10 A test strips – risk of falsely low results when measuring test strips on the Urisys 1100 urine analyser

Article citation: Drug Safety Update volume 11, issue 12; July 2018: 7.
