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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In our first article, we inform of the Commission on Human Medicine's (CHM) recommendations for the yellow fever vaccine following a detailed review of the benefits and risks (page 2). The review found that for most people, the balance of benefits and possible side effects remains overwhelmingly favourable. However, CHM recommended strengthened measures to reduce the risk of serious side effects in those who may have a weaker immune system. Key recommendations include new and updated contraindications, further precautions for use in individuals aged 60 years or older, and standardised risk-benefit evaluation procedures across UK yellow fever vaccination centres to ensure that people only receive the vaccine after a thorough risk assessment.

On page 5, we advise prescribers of carfilzomib for multiple myeloma of the risk of hepatitis B reactivation during treatment. Screening for hepatitis B virus serology is necessary before initiation of carfilzomib and in any patients currently undergoing treatment with carfilzomib.

Finally, see pages 7 to 9 for a list of recent alerts and letters about medicines and medical devices, including an overview of recent recalls of ranitidine medicines due to possible contamination with N-nitrosodimethylamine (NDMA), an impurity that has genotoxic and carcinogenic potential.

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Yellow fever vaccine: stronger precautions in people with weakened immunity and in those aged 60 years or older

The Commission on Human Medicines has issued a series of recommendations to strengthen measures to minimise risk with the yellow fever vaccine (Stamaril) following very rare fatal reactions. Key recommendations include new and updated contraindications and strengthened precautions to protect those with a weakened immune systems (including for people aged 60 years or older) and standardised risk-benefit evaluation procedures across UK yellow fever vaccination centres to ensure that people only receive the vaccine after a thorough risk assessment.

Advice for healthcare professionals:

- yellow fever vaccine is a highly effective vaccine to protect against life-threatening yellow fever infection; however, strict adherence to contraindications and precautions is essential to reduce the risk of very rare but potentially fatal adverse reactions
- following a review of the benefits and risks of the vaccine, the Commission on Human Medicines (CHM) has made recommendations to strengthen measures to minimise risk
- key recommendations include new and updated contraindications, strengthened precautions for use in individuals aged 60 years and older, and standardised risk-benefit evaluation procedures across UK yellow fever vaccination centres to ensure that people only receive the vaccine after a thorough risk assessment
- a letter from MHRA, Public Health England, National Travel Health Network and Centre (NaTHNaC), and Health Protection Scotland has been sent to UK yellow fever vaccination centres to inform them of the recommendations and that changes will be made to the product information and standardised pre-vaccination screening tools
- only healthcare professionals specifically trained in benefit-risk evaluation of yellow fever vaccine should administer the vaccine, following their individualised assessment of a person's travel itinerary and suitability to receive the vaccine
- every vaccinee should be advised to seek emergency medical attention if they develop signs or symptoms of very rare neurotropic disease (YEL-AND) or viscerotropic disease (YEL-AVD) and should receive the manufacturer's patient information leaflet as part of the travel consultation

Yellow fever vaccine

Yellow fever is a life-threatening viral infection and protective measures against the disease are essential for anyone travelling to an area where there is a risk of infection. Yellow fever vaccine (Stamaril) is highly effective and is the best way to protect those at risk of disease during travel.

For most people, the balance between the benefits and possible side effects of the vaccine remains overwhelmingly favourable. However, because the vaccine contains a live, weakened strain of the yellow fever virus, strict adherence to contraindications and precautions is essential to reduce the risk of serious side effects in those who may have a weaker immune system.

Revaccination is generally not recommended as the duration of protection following administration of 1 dose of yellow fever vaccine is expected to be lifelong.

Very rare risks associated with yellow fever vaccine

Two risks unique to yellow fever vaccine are viscerotropic disease (YEL-AVD) and neurotropic disease (YEL-AND), which both resemble yellow fever infection. These are very rare but can be fatal. At vaccination all vaccinees should receive the manufacturer's patient information leaflet for Stamaril vaccine, which advises them on symptoms to be vigilant for following vaccination.

These risks are more likely to occur in certain groups, particularly people with a weakened immune system, people without a thymus, and people aged 60 years or older. The risks of YEL-AND and YEL-AVD are estimated to be up to 1 per 100,000 primary vaccinees, although this may be up to 4-times greater in those aged 60 years or older.

Presentation of YEL-AND

Cases of neurotropic disease (YEL-AND) have been reported in primary vaccinees with an onset within 30 days of vaccination. The risk appears to be higher in people older than 60 years and younger than 9 months of age (including infants exposed to vaccine through breastfeeding), although cases have been also reported in other age groups. Congenital or acquired immunodeficiency has also been recognised as a potential risk factor.

YEL-AND may manifest as high fever with headache that may progress to include 1 or more of confusion, lethargy, encephalitis, encephalopathy, and meningitis. Other neurological signs and symptoms have been reported and include convulsions, Guillain-Barré syndrome, and focal neurological deficits.

Presentation of YEL-AVD

Cases of viscerotropic disease (YEL-AVD; formerly described as febrile multiple organ-system failure) have been reported following vaccination with yellow fever vaccine, some of which have been fatal. In most cases reported, the onset of signs and symptoms was within 10 days of vaccination.

Initial signs and symptoms of AVD are non-specific and may include pyrexia, myalgia, fatigue, headache and hypotension, potentially progressing quickly to liver dysfunction with jaundice, muscle cytolysis, thrombocytopenia, and acute respiratory and renal failure.

Trigger for detailed review and recommendations

Recent fatal cases of YEL-AVD in the UK prompted the UK's Commission on Human Medicines (CHM) to convene an Expert Working Group in 2019 to consider the balance of benefits and risks of yellow fever vaccine, risk factors for serious adverse reactions, and the measures in place in the UK to minimise risks. While the review was ongoing, advice to healthcare professionals was issued that extreme caution was needed in people who were immunosuppressed and in people aged 60 years and older (see Drug Safety Update April 2019).

The review considered published data and vaccine adverse events reported to the MHRA, the manufacturer, and incidents reported through National Travel Health Network and Centre (NaTHNaC) and Health Protection Scotland (HPS). A full report of the review and evidence base for the recommendations is available.

This review concluded in October 2019, and CHM has now issued a set of updated recommendations to minimise risks to vaccinees. The recommendations are in addition to the full list of contraindications and precautions described in the current Summary of Product Characteristics and Patient Information Leaflet, which will be updated. Standardised pre-vaccination screening checklists are also being produced, along with a patient group direction template. A further communication will be issued once these documents are ready to ensure they can be implemented in clinical practice.

The key recommendations of the review can be found in the letter from MHRA, PHE, NaTHNaC, and HPS, which was sent to vaccination clinics on 21 November 2019.

Background

More than 600 million doses of yellow fever vaccine have been used worldwide since the 1930s. Stamaril (Sanofi Pasteur) is the only licensed yellow fever vaccine available in the UK.

Report suspected reactions to vaccines

Please continue to report suspected adverse reactions to vaccines and other medicines to the Yellow Card Scheme. When reporting a suspected reaction to a vaccine, please provide the brand name (or product licence number and manufacturer) and the specific batch number. Additionally, when providing patients with details of the vaccine administered, it is good practice to give them details of the brand and batch number. This will allow patients and carers to more accurately report suspected reactions to the Yellow Card Scheme.

Incidents involving the yellow fever vaccine in England, Wales, and Northern Ireland should be reported to NaTHNaC and incidents in Scotland should be reported to HPS.

Any medication error (for example, vaccination of a contraindicated person) that results in harm should be reported via the Yellow Card Scheme. Medication errors in the absence of harm should be reported via local reporting methods

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Carfilzomib (Kyprolis▼): risk of reactivation of hepatitis B virus

Establish hepatitis B status before initiating carfilzomib and in patients with unknown hepatitis B virus serology who are already being treated with carfilzomib.

Advice for healthcare professionals:

- hepatitis B virus reactivation has been reported in patients treated with carfilzomib
- screen all patients for hepatitis B virus before initiation of carfilzomib; patients with unknown serology who are already on treatment should also be screened
- consider prophylaxis with antivirals for patients with positive serology who are treated with carfilzomib
- monitor patients with positive serology for clinical and laboratory signs of hepatitis B reactivation during and after treatment
- advise patients with positive serology to seek medical help immediately if they experience signs and symptoms suggestive of hepatitis B virus reactivation
- in patients who have hepatitis B reactivation, it is recommended to consult relevant experts when making decisions regarding hepatitis B virus treatment and the continuation, interruption, or resumption of carfilzomib
- report any suspected adverse drug reactions associated with carfilzomib to the Yellow Card Scheme

Review of cases of hepatitis B reactivation

Carfilzomib (Kyprolis▼) is indicated in combination with lenalidomide and dexamethasone or with only dexamethasone for the treatment of adult patients with multiple myeloma who have received at least 1 prior therapy.

A recent EU review of clinical studies and cases of suspected adverse drug reactions has identified reports of hepatitis B reactivation associated with carfilzomib. Following the review, changes are being made to the Summary of Product Characteristics to recommend screening for hepatitis B virus before a patient starts carfilzomib treatment. Screening is also recommended for patients already under treatment with carfilzomib with unknown hepatitis B virus serology.

Details of cases reported

The review assessed cases worldwide up to 10 July 2019 and identified a total of 23 cases from clinical studies and post-marketing.

In clinical studies, 8 serious cases of hepatitis B virus reactivation were identified. Of these, 5 cases had a plausible temporal association and liver function abnormalities and reported an improvement in the patient's clinical condition once the medicine was stopped (positive dechallenge).

The review also identified 15 cases of hepatitis B virus reactivation in the post-marketing period. Most of these cases (93%; 14 cases) were serious.

1. Provided to the MHRA by Amgen. October 2019. Exposure is cumulative from 20 July 2012 (the date the product was first authorised worldwide).

Reactivation was reported in 12 men and 3 women, with a median patient age of 70 years (range 41 to 78 years). The worldwide cumulative post-marketing exposure for carfilzomib is approximately 108 900 patients (42 200 patient-years) up to 19 January 2019.[1]

Of the 13 post-marketing cases in which baseline serology was reported: 3 cases were positive for hepatitis B core antibodies (anti-HBc), 5 cases were negative for hepatitis B surface antigen (HBsAg), 1 case had negative anti-HBc, and 4 had undetected hepatitis B DNA. After diagnosis of hepatitis B virus reactivation, positive HBsAg was reported in 3 cases, with hepatitis B DNA elevated in 4 cases.

Most cases (80%;12) had a plausible temporal association. In 5 cases, the reports indicated the patients' clinical condition improved once the medicine was stopped, and in 1 case, worsened again once the medicine was restarted. 11 patients received treatment with an anti-hepatitis B medicine. In 5 cases, carfilzomib treatment was continued, and the patient recovered from the hepatitis infection.

Report any suspected adverse drug reactions

Carfilzomib is subject to additional monitoring and any suspected adverse drug reactions (ADR) should be reported to the Yellow Card Scheme. Report on the Yellow Card website or via the Yellow Card app (download via iTunes Yellow Card for iOS devices or via PlayStore Yellow Card for Android devices).

Reporting suspected ADRs, even those known to occur, 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.

Article citation: Drug Safety Update volume 13, issue 4: November 2019: 2.

Letters and drug alerts sent to healthcare professionals in October 2019

Letters sent in October 2019

- Volibris (ambrisentan): new patient alert card and removal of the controlled distribution system
- Quadrivalent Influenza Vaccine (split virion, inactivated): Supply of Standard Export packs Lot T3H244M
- Fentanyl 50 micrograms/ml (10ml ampoules): non-UK marketing authorisation number on the label of batch 0112391R

Ranitidine: pharmacy-level recalls

There has been a number of pharmacy-level recalls for ranitidine-containing products as a precautionary measure due to possible contamination with N-nitrosodimethylamine (NDMA), an impurity which has genotoxic and carcinogenic potential. This impurity was also detected in sartan medicines, leading to their recall earlier this year.

This is an ongoing issue and the MHRA is actively involved with the European Medicines Agency and with other medicines regulators. An investigation into other potentially impacted products is continuing and further updates will be provided as the investigation progresses. At the time of publication, class 2 recalls have been issued for the following products:

- Zantac Injection 50mg/2ml, Zantac Syrup 150mg/10ml, Zantac Tablets 150mg, Zantac Tablets 300mg (EL (19)A 24), manufactured by GlaxoSmithKline, trading as Glaxo Welcome. Issued 8 October 2019
- Ranitidine Effervescent Tablets 150mg, Ranitidine Effervescent Tablets 300mg (EL (19)A/27), manufactured by Teva UK. Issued 17 October 2019
- Zantac 75 Relief Tablets, Zantac 75 Tablets, Galpharm Indigestion Relief 75mg Tablets, Boots Heartburn & Indigestion Relief 75mg Tablets, Kirkland Indigestion Relief 75mg Tablets, Morrisons Indigestion & Heartburn Relief 75mg Tablets, Boots Heartburn & Indigestion Relief 75mg Tablets (EL (19)A/30), manufactured by Omega Pharma, trading as Perrigo, and Galpharm International (part of the Perrigo Group). Issued 25 October 2019
- Ranitidine 150mg/10ml Oral Solution (EL (19)A/29), manufactured by Rosemont Pharmaceuticals (part of the Perrigo Group). Issued 25 October 2019
- Ranitidine Oral Solution 30mg/ml, Ranitidine 150mg Tablets (EL(19)A/36), manufactured by Creo Pharma and Tillomed Laboratories. Issued 19 November 2019
- Ranitidine 75mg Tablets, (Various Liveries) (EL(19)A/37), manufactured by OTC Concepts, Relconchem and Noumed Life Sciences, and Medreich. Issued 21 November 2019

Pharmacies are advised to stop supplying affected products immediately and to return them to their supplier. If patients are concerned, advise them to contact their GP, pharmacist, or healthcare professional to review ongoing treatment. The Department of Health and Social Care issued a Supply Distribution Alert (SDA/2019/005) for all oral formulations of ranitidine on 15 October 2019.

Other recalls

Class 2 medicines recall: Sayana Press 104mg/0.65ml (MDR 055-06/19). Issued 23 October 2019. Pfizer is recalling certain batches of Sayana Press (medroxyprogesterone acetate) suspension for subcutaneous injection. This is because of an issue related to the sealing process that may impact the integrity of the product. Affected batches should be returned to the supplier.

Class 2 medicines recall: Nutriflex Omega Plus 1250ml, 1875ml and 2500ml, and Nutriflex Omega Special 625ml, 1250ml, 1875ml and 2500ml, and Supplemented Product codes ASNSPOMCA, ASNSPOMSVA, ASNPLOMCA, ASNPLOMSVA (625ml, 1250ml, 1875ml 2500ml) (EL(19)A/31). Issued 30 October 2019. B Braun is initiating a recall of certain batches of the above products as a precautionary measure. This is because ongoing product monitoring has identified that some bags may not comply with the required specification throughout the product shelf-life.

Company-led drug alert: Avonex 30 micrograms/0.5ml Solution for Injection. Issued 23 October 2019. Biogen Idec UK is recalling batches of Avonex at wholesaler, pharmacy, and homecare provider level due to a manufacturing issue. The issue could potentially have resulted in a loss of sterility assurance and may have weakened the glass structure of the syringe with the possible formation of particulate matter.

Company-led drug alert: Docetaxel Injection 80mg /8ml. Issued 22 October 2019. Pfizer UK is recalling batches as routine stability testing has identified that levels of a known impurity, 10-oxo-docetaxel, may exceed the acceptable level at end of shelf-life.

Defect information

Class 4 Medicines Defect Information: Xonvea 10 mg/10 mg gastro-resistant tablets (MDR 025-10/19). Issued 16 October 2019. Some side effects documented in the Summary of Product Characteristics for Xonvea (manufactured by Alliance Pharmaceuticals) are not included in the Patient Information Leaflet provided with listed batches. These include antihistamine anticholinergic effects and rarely, effects on white blood cell production. If dispensing a listed batch, healthcare professionals are asked to ensure patients are aware of the missing information. Newly released batches on the market will include the updated patient leaflet.

Class 4 Medicines Defect Information: Rifadin (rifampicin) 150mg Capsules (MDR 127-09/19). Issued 16 October 2019. The Patient Information Leaflet for the listed batch of Rifadin 150mg capsules does not several important side effects. If dispensing from the listed batch, please remove the leaflet and replace with the updated version.

In October a Class 4 Medicines Defect Information alert was also issued for Emerade 150, 300 and 500 microgram solution for injection in pre-filled syringe (MDR 57-08/19) See Drug Safety Update October 2019 for more information.

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Medical Device Alerts issued in October 2019

In this monthly update, we highlight selected Medical Device Alerts and notices 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.

- Rocket and NuSurgix fetal blood sampling (FBS) amnioscopes and FBS kits: stop using ethyl chloride spray during the fetal blood sampling procedure with these devices (MDA/2019/035). Issued 9 October 2019. Manufactured by Rocket Medical and NuSurgix. Potential incompatibility between ethyl chloride spray and the device. Ethyl chloride spray should not be used with Rocket Medical or NuSurgix amnioscopes.

- Professional use defibrillator/monitor: Efficia DFM100 (Model number 866199) – risk of failure to switch on or unexpected restart (MDA/2019/039). Issued 31 October 2019. Manufactured by Philips – due to a software or hardware issue the device may fail to start or deliver defibrillation therapy. Affected devices should be identified and recommended actions carried out. Backup defibrillators should be available until the software and hardware upgrades have been undertaken.

- Syringe driver pumps: T34 3rd edition models only – stop using the pump until updated instructions for use and BodyCommTM V3.0 software are released (MDA/2019/038). Issued 31 October 2019. Manufactured by CME (a BD company) – the intended operation of these pumps cannot be verified due to errors in the instructions for use (IFUs) and the incompatibility with older versions of BodyComm software (88-102). Identify patients currently receiving treatment supported by these pumps and assist them to discontinue using the device when clinically appropriate. If there is no alternative device available and it is not clinically appropriate to discontinue use, a risk assessment should be conducted and documented.

Risk of false-low biochemistry test results with multiple assays manufactured by Beckman Coulter in acetaminophen overdose

Healthcare professionals may also wish to be aware of a recent notice from Beckman Coulter to laboratories using listed assays. N-acetyl-p-benzoquinone imine (NAPQI), a metabolite of acetaminophen (paracetamol), may cause negative interference for enzymatic creatinine, triglycerides GPO blanked, uric acid, direct bilirubin, and total bilirubin testing in toxicity/overdose of acetaminophen. Acetaminophen itself is not thought to interfere with the assays.

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