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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The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for ensuring that medicines and medical devices work and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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First, we ask healthcare professionals to be vigilant for any suspected side effects or safety concerns associated with e-cigarette use or vaping (including lung injury) and report them to the MHRA via the Yellow Card Scheme. In the article on page 2 we provide UK case definitions of e-cigarette or vaping associated lung injury (EVALI) to facilitate identification.

Next, we advise of recent epidemiological studies suggesting exposure to ondansetron during the first trimester of pregnancy is associated with a small increased risk of the baby having a cleft lip and/or cleft palate (page 6).

Finally, we advise prescribers of mecasermin for severe primary insulin-like growth factor 1 (IGF-1) deficiency of benign and malignant neoplasms observed in some children and adolescents who received treatment. Mecasermin should not be used in children or adolescents with active or suspected neoplasia or with any condition or medical history that increases the risk of benign or malignant neoplasia (page 8).

drugsafetyupdate@mhra.gov.uk

E-cigarette use or vaping: reporting suspected adverse reactions, including lung injury

Be vigilant for any suspected adverse reactions associated with use of e-cigarettes or vaping (including lung injury) and report them to the MHRA via the Yellow Card Scheme.

Information for healthcare professionals:

- the US Centers for Disease Control and Prevention (CDC) and its public health partners are investigating cases of lung injury associated with the use of e-cigarette or vaping products. At the time of publication, more than 2600 US cases have been identified (60 fatal cases), but the outbreak seems to be in decline
- the CDC has identified vitamin E acetate as a chemical of concern, although evidence is not yet sufficient to exclude other substances of concern and it may be that there is more than one cause
- as of January 2020, MHRA is aware of two potential cases of e-cigarette or vaping associated lung injury in the UK (one reported as a Yellow Card), both of which were reported as having a fatal outcome

Actions needed from healthcare professionals:

- have a high index of suspicion in patients presenting with respiratory symptoms where there is a history of e-cigarette use or vaping in the past 30 days
- use the Yellow Card Scheme website to report any suspected side effects or safety concerns with e-cigarettes and the e-liquids used for vaping
- for all patients, ask about e-cigarette use or vaping routinely as you would do about cigarette smoking (see Advice to routinely document history on page 3)

www.mhra.gov.uk/yellowcard

E-cigarette use or vaping associated lung injury: background

Authorities in the USA are investigating a multistate outbreak of e-cigarette or vaping associated lung injury, also known as EVALI (see Description of US cases on page 3). The US outbreak peaked in summer 2019 and at the time of publication, the outbreak in the USA seems to be in decline.

www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html

Currently, the volume and pattern of adverse respiratory events reported in association with e-cigarette use or vaping in the UK do not seem to reflect the trends emerging from the USA. This difference of magnitude may be due to differences in regulations, nicotine strengths available, chemical substances and devices used, and proportional use by younger populations. However, it may also be due to a lower index of suspicion among healthcare professionals in the UK.

As of January 2020, MHRA has received one Yellow Card report of EVALI in the UK, occurring during a similar time period to the US outbreak. The Yellow Card report includes sufficient data to suggest similarities to EVALI cases in the USA (in terms of meeting the US criteria[1] for a case of EVALI, the symptoms and investigation findings and clinical progression), although further details are being sought. The MHRA has also been informed of another potential case of lung injury relating to vaping in this time period (January 2019 to January 2020). Both of these cases were reported as having a fatal outcome.

1. US Centers for Disease Control and Prevention. Information accessed 6 January 2020.

Prompt reporting of suspected adverse reactions, including probable or possible cases of e-cigarette or vaping associated lung injury (EVALI), to the Yellow Card Scheme will assist the MHRA to take action as necessary to protect public health in case of the emergence of a similar situation as in the USA.

Description of US cases

From March 2019 to January 2020, more than 2600 cases of EVALI and 60 associated deaths were reported in the USA (for latest information see the CDC).[1] Where data on hospitalisation status are known, 95% of cases were hospitalised and a proportion required intensive care.[2,3] Most cases presented with non-specific respiratory symptoms such as cough, dyspnoea (shortness of breath), and chest pain, often with associated gastrointestinal symptoms, fever, chills and weight loss.[3,4]

Radiological findings include pulmonary infiltrates on chest X-rays and bilateral ground glass infiltrates on CT thorax.[3] The CDC considers some chronic conditions, including cardiac disease, chronic respiratory disease, and diabetes, as well as increasing age, to be potential risk factors for rehospitalisation and death.[1,5]

The CDC states that most cases (86%) reported the use of tetrahydrocannabinol (THC).[1] A small proportion of cases (11%) report use of nicotine liquids exclusively.[1] THC is illegal in the UK under the Misuse of Drugs Act (1971). Vitamin E acetate, used as an additive in THC-containing vaping products, has been identified by the CDC as a chemical of concern.[1,6] However, evidence is insufficient to rule out the contribution of other chemicals and there may be more than one cause.[1] Vitamin E, along with other vitamins, is not permitted as an ingredient in notifiable nicotine e-cigarettes or e-liquids in the UK (see UK context and cases below).

The underlying pathology or mechanisms contributing to lung injury remain unknown. Pathologies described include lipoid pneumonia,[7] chemical pneumonitis,[8] giant cell interstitial pneumonitis,[9] and hypersensitivity pneumonitis.[9]

UK context and cases

It is estimated that 3.6 million people use e-cigarettes in the UK. Nicotine-containing e-cigarettes and e-liquids have been regulated since the introduction of the Tobacco and Related Products Regulations (TRPR) in 2016. The MHRA is the competent authority for the notification scheme in the UK.

The regulations include requirements for notification, including submission of data relating to ingredients and emissions to the MHRA, annual reporting, product information, labelling and vigilance, as well as restrictions on advertising. The TRPR ban certain ingredients including vitamins, colourings, caffeine, and taurine, as well as ingredients that are known to have carcinogenic, mutagenic or reprotoxic (CMR) properties. In addition to this, MHRA has published ingredients guidance listing substances that should not be included in e-cigarettes and refill containers due to their known risk to human health. it is illegal to sell e-cigarettes or e-liquids to anyone under the age of 18 years.

As of 8 January 2020, we are aware of 244 suspected adverse reaction reports (182 relating to respiratory terms) to the MHRA's Yellow Card Scheme and received via industry associated with e-cigarettes or e-liquids. Of these, 20 reports describe 27 serious respiratory events including lipoid pneumonia, hypersensitivity pneumonitis, pulmonary fibrosis, pleural effusion, pneumothorax, lower respiratory tract infection, and infectious pneumonia. Four Yellow Card reports included a fatal outcome. However, not all are considered to be causally associated. Two of these reports were received between January 2019 and January 2020; one reports EVALI as discussed in Background (page 2).

2. Chatham-Stephens K, et al. MMWR Morb Mortal Wkly Rep 2019; 68: 1076–1080.

3. Siegel D, et al. MMWR Morb Mortal Wkly Rep 2019; 68: 919–27.

4. Layden, JE, et al. N Engl J Med 2019. Published online 6 September. DOI: 10.1056/NEJMoa1911614.

5. Mikosz C, et al. MMWR Morb Mortal Wkly Rep 2020; 68: 1183–88.

6. Lewis N, et al. MMWR Morb Mortal Wkly Rep 2019; 68: 953–56.

7. Davidson K, et al. MMWR Morb Mortal Wkly Rep 2019; 68: 784–86.

8. Butt YM, et al. N Engl J Med 2019; 381: 1780–81.

9. Henry T, et al. N Engl J Med 2019; 381: 1486–87.

https://www.gov.uk/guidance/e-cigarettes-regulations-for-consumer-products

Case definitions of e-cigarette or vaping associated lung injury

Since there are no standard diagnostic criteria, on the basis of expert advice, we have devised UK case definitions of e-cigarette or vaping associated lung injury to facilitate identification.

Cases should be considered **probable** if they meet ALL of the following criteria:

1. Using an e-cigarette or vaping in 30 days prior to symptom onset
   AND
2. Pulmonary infiltrate, such as opacities on plain-film chest X-ray, or ground glass opacities on CT chest
   AND
3. Absence of respiratory infection. Minimum criteria to be excluded:
   - Negative respiratory viral screen (eg, influenza, adenovirus, rhinovirus, coronavirus)
   - Negative testing for all other clinically-indicated respiratory infectious diseases (eg, urine antigen for Streptococcus pneumoniae and Legionella, sputum culture, bronchoalveolar lavage culture, blood culture and opportunistic respiratory infections if appropriate)

   AND
4. No evidence of alternative diagnosis (eg, cardiac, autoimmune, malignancy)

Cases should be considered **possible** if they meet criteria 1, 2, and 4, but a respiratory infection is identified via culture or PCR, and the clinical team believes infection is not the only cause of underlying lung injury OR the minimum criteria to exclude infection are not met due to testing not having been performed and the clinical team believes the infection is not the only cause of the underlying lung injury.

Cases that do not strictly meet the criteria, for example if use of e-cigarette or vaping stopped more than 30 days before symptom onset, are still of interest and should be reported.

How to report suspected side effects or safety concerns to the Yellow Card Scheme

Report any suspected side effects or safety concerns with e-cigarettes and e-liquids via the e-cigarette reporting tool for the electronic Yellow Card Scheme. Information provided to the Yellow Card Scheme is kept safe, secure and confidential.

https://yellowcard.mhra.gov.uk/yellowcards/tobaccoreportmediator/

If you report a case of EVALI, please specify if it meets the criteria for a probable or possible case and provide full details of the vaping product, vaping history, and other potentially relevant clinical details, including combustible cigarette smoking history, and investigation results. If a product sample is available for analysis, please also specify this via the Yellow Card report.

In response, we may contact you to collect further details regarding the case via this form. The form should be returned to yellowcard@mhra.gov.uk or to Freepost Yellow Card Scheme (no other address details or postage required).

The form is also available here: PDF and Word document version.

Routinely document e-cigarette history

As part of routine clinical practice, clinicians are advised to document use of e-cigarettes or vaping devices in medical records for all patients as they would with smoking.

Clinicians should routinely document:

- Name or brand of product used
- Type of product (if known)
- Duration and frequency used
- Substances vaped (for example, nicotine or recreational substances)
- Strengths of substances

Publication notice

The information in this article reflects understanding at the time of publication in January 2020. This is an emerging issue and clinicians are advised to remain engaged with further information from the MHRA, public health bodies, and other sources around this enhanced surveillance scheme and safety information for electronic cigarettes.

Article citation: Drug Safety Update volume 13, issue 6: January 2020: 1.

Ondansetron: small increased risk of oral clefts following use in the first 12 weeks of pregnancy

Recent epidemiological studies suggest exposure to ondansetron during the first trimester of pregnancy is associated with a small increased risk of the baby having a cleft lip and/or cleft palate.

Ondansetron: evidence and advice

Ondansetron (Zofran), a 5-HT3 receptor antagonist, is authorised for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy (in adults and children older than 6 months) and for the prevention and treatment of nausea and vomiting after surgery (in adults and children older than 1 month).

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. There is a growing body of evidence on the use of ondansetron in pregnancy that does not suggest an increase in the risk of overall congenital malformations combined (for example publications[1,2,3]).

Recent epidemiological studies report a small increased risk of orofacial malformations in babies born to women who used ondansetron in early pregnancy.[1,4] Key evidence was an observational study of 1.8 million pregnancies in the USA of which 88,467 (4.9%) were exposed to oral ondansetron during the first trimester of pregnancy. The study reported that ondansetron use was associated with an additional 3 oral clefts per 10,000 births (14 cases per 10,000 births versus 11 cases per 10,000 births in the unexposed population).[1] These data were recently reviewed within Europe and considered to be robust. As for all licensed medicines, the safety of ondansetron will be continuously monitored by the MHRA and relevant emerging information will be considered as it becomes available.

Outside of its authorised indications, ondansetron is also used second line for treating women with hyperemesis gravidarum, a severe and potentially life-threatening condition.[5] If a physician considers, based on their professional judgement, the available evidence and the risks for mother and baby of malnutrition in early pregnancy, that a licensed treatment (for example doxylamine/pyridoxine, Xonvea[6]) is not suitable or not sufficient alone to control severe nausea and vomiting in pregnancy, and there is a special clinical need to use ondansetron, then this decision should be made in consultation with the patient after she has been fully informed of the potential benefits and risks of the different treatment options.

Prescribers should refer to clinical guidance if treatment with ondansetron is considered for severe nausea and vomiting in pregnancy.[5]

Detailed findings of studies

A retrospective cohort study[1] of a medical claims database in the USA included 1,816,414 pregnancies between 2000 and 2013, of which 88,467 (4.9%) were associated with a prescription of ondansetron during the first trimester. Exposure to ondansetron during the first 12 weeks of pregnancy was linked with a small but statistically significant increased risk of orofacial cleft defects (adjusted relative risk [aRR] 1.24, 95% CI 1.03–1.48).

1. Huybrechts KF, et al. *JAMA* 2018; 320: 2429–37.

2. Lavecchia M, et al. *J Obstet Gynaecol Can* 2018; 40: 910–18.

3. Kaplan YC, et al. *Reprod Toxicol* 2019; 86: 1–13.

4. Zambelli-Weiner A, et al. *Reprod Toxicol* 2019; 83: 14–20.

5. Royal College of Obstetrics and Gynaecology. Green-top Guideline No. 69. June 2016.

6. Xonvea [doxylamine succinate, pyridoxine hydrochloride] is authorised for treatment of nausea and vomiting in pregnancy for patients who do not respond to conservative management.

A case–control study of another US medical claims database[4] included 864,083 mother-infant pairs seen between 2000 and 2014, and found a non-statistically significant trend towards an increased risk of orofacial cleft defects in babies exposed to ondansetron compared with those not exposed to any antiemetic (adjusted odds ratio [OR] 1.30, 95% CI 0.75–2.25). This study also linked ondansetron use during the first trimester with an increased risk of cardiac defects (adjusted OR 1.43, 95% CI 1.28–1.61).[4] However, this finding conflicts with results from other studies. For example, Huybrechts and colleagues[1] did not find a significant association for cardiac defects after adjusting for pre-defined confounding factors (aRR 0.99, 95% CI 0.93–1.06).

The recent observational studies have some limitations inherent to the data sources, but the findings are considered sufficiently robust to indicate that use of ondansetron during the first trimester of pregnancy is associated with a small increased risk of the baby having a cleft lip and/or cleft palate.

If the clinical decision is to offer ondansetron in pregnancy, women must be counselled on the potential benefits and risks of use, both to her and to her unborn baby and the final decision should be made jointly.

Report adverse drug reactions in pregnancy

Report any suspected adverse drug reactions in the mother or child, including adverse pregnancy outcomes, following use of a medicine in pregnancy on a Yellow Card.

All healthcare professionals, patients, parents, and caregivers can report any suspected adverse reactions associated with medicines to the Yellow Card Scheme.

It is easy to report on the Yellow Card website or via the Yellow Card app. Download the App via iTunes Yellow Card for iOS devices or via PlayStore Yellow Card for Android devices.

Article citation: Drug Safety Update volume 13, issue 6: January 2020: 2.

Mecasermin (Increlex▼): risk of benign and malignant neoplasia

Cases of benign and malignant neoplasms have been observed among children and adolescents who received treatment with mecasermin. Do not use mecasermin in children or adolescents with active or suspected neoplasia or with any condition or medical history that increases the risk of benign or malignant neoplasia.

Advice for healthcare professionals:

- cases of benign and malignant neoplasms have been observed among children and adolescents who received treatment with mecasermin
- permanently discontinue mecasermin if a benign or malignant neoplasm develops
- mecasermin is contraindicated in children and adolescents with active or suspected neoplasia and in any condition or medical history that increases the risk of benign or malignant neoplasia
- mecasermin is licensed only for the treatment of severe primary insulin-like growth factor 1 (IGF-1) deficiency and the recommended maximum dose is 0.12 mg/kg given twice daily – data suggest the risk of neoplasia is higher when used outside of the licensed indication or dose (see details below)
- report all suspected adverse drug reactions associated with the use of mecasermin to the Yellow Card Scheme

Background

Mecasermin is a recombinant human insulin-like growth factor 1 (rh-IGF-1). It is indicated for the long-term treatment of growth failure in children and adolescents aged 2–18 years with confirmed severe primary insulin-like growth factor 1 deficiency (primary IGFD). The recommended maximum dose is 0.12 mg/kg given twice a day.

Review of cases of neoplasia

An EU review identified an increased incidence of benign and malignant tumours in patients receiving mecasermin in the post-marketing setting compared with the background incidence in this patient population. These cases represented a variety of different malignancies and included rare cancers not usually seen in children. Most cases occurred in patients treated outside the authorised indication or exceeding the maximum dose, however some were reported within the authorised indication and posology for mecasermin.

Increlex (mecasermin): risk of benign and malignant neoplasia. Letter to healthcare professionals.

Current knowledge of IGF-1 biology suggests that IGF-1 may play a role in malignancies within all organs and tissues. The role of the IGF family in the genesis of human benign and malignant neoplasia has been observed in several epidemiological and pre-clinical studies. Physicians should therefore be vigilant for any potential malignancy. Mecasermin is already contraindicated in active or suspected neoplasia. Following the review, the contraindication will be expanded to children or adolescents with any condition or medical history that increases the risk of benign or malignant neoplasia, and this will be added into the product information. A letter has also been sent from the manufacturer to prescribers and dispensers of mecasermin.

In rare situations where a physician considers that that there is a special clinical need to use mecasermin outside of the licensed indication or recommended posology, then this decision should be made in consultation with the patient and caregivers after they have been fully informed of the potential benefits and risks. Physicians should be particularly vigilant for any potential malignancies in these situations.

Reporting suspected adverse drug reactions to mecasermin

Suspected adverse drug reactions associated with use of mecasermin should be reported to the Yellow Card Scheme. Healthcare professionals are asked to report all adverse drug reactions suspected to be associated with black triangle products through the Yellow Card Scheme.

Article citation: Drug Safety Update volume 13, issue 6: January 2020: 3.

Letters and drug alerts sent to healthcare professionals in December 2019

Insuman – permanent discontinuation of 3 presentations

In December 2019, Sanofi issued a letter to healthcare professionals to inform of a permanent discontinuation of 3 presentations of Insuman (recombinant human insulin).

- Insuman Comb 15 100 IU/mL - suspension for injection in a cartridge
- Insuman Basal 100 IU/mL - suspension for injection in a vial
- Insuman Comb 25 100 IU/mL - suspension for injection in a vial

Since supply is due to end in 2020, the letter recommends that no new patients should be started on the listed presentations and replacement with alternative insulin formulations initiated. Switching of insulins should be done under the supervision of a healthcare professional who can provide training on how to use the new delivery device (pen); blood glucose levels should be closely monitored while the patient becomes familiar with their new product.

Update - Valproate Pregnancy Prevention Programme

Healthcare professionals involved in the care of female patients on valproate medicines in the UK should be vigilant for the arrival of letters from Sanofi containing updated educational materials. Continue to use these educational materials to ensure women and girls of childbearing potential on valproate medicines meet the requirements of the Pregnancy Prevention Programme.

- Letter for all pharmacists dispensing valproate medicines
- Letter for specialists and specialist nurses, general practitioners, and other healthcare professionals who provide care to patients treated with valproate medicines

In 2019 the Annual Risk Acknowledgement Form and Guide for Healthcare Professionals were updated in collaboration with the MHRA after involvement with other stakeholder groups. Also updated are the Patient Card and Patient Guide to be provided to female patients on valproate medicines. Pharmacies are also advised of the updated dispensary poster and white box warning labels. Changes in the materials were made to clarify the existing regulatory situation and not due to new advice.

The letters containing the materials are being distributed to specialists and other healthcare professionals (via post) and pharmacies (via Tote boxes) in January 2020. For more about the Valproate Pregnancy Prevention Programme, see Drug Safety Update from April 2018.

Ranitidine – further recalls

Previously we highlighted recalls for ranitidine medicines due to possible contamination with an impurity N-nitrosodimethylamine (NDMA), which has genotoxic and carcinogenic potential. In December 2019, two recalls were issued for ranitidine medicines.

- Class 2 Medicines Recall: Medley Pharma Limited, Ranitidine 150mg Tablets BP, PL 43870/0026, Ranitidine 300mg Tablets BP, PL 43870/0027 (EL(19)A/41). Issued 16 December 2019. Medley Pharma is recalling all unexpired stock of the listed products from pharmacies and retail stores as a precautionary measure.

- Class 2 Medicines recall: Ranitidine 150mg Film-Coated Tablets, PL 20075/0063, Ranitidine 300mg Film-Coated Tablets, PL 20075/0064 (EL(19)A/40). Issued 5 December 2019. Accord Healthcare are recalling all unexpired stock from pharmacies and retail stores.

Other alerts from December 2019

Company led drug alert – Paclitaxel 6 mg/ml concentrate for solution for infusion (25ml vials). Issued 19 December 2019. Hospira UK (Pfizer) is recalling specific batches as a precautionary measure.

Article citation: Drug Safety Update volume 13, issue 6: January 2020: 4.

Medical Device Alerts issued in December 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.

Arrow EZ-IO intraosseous vascular access needle sets – risk of needle stick injury. Issued 19 December 2019. Manufactured by Teleflex Medical (Arrow) – do not use needles if the safety cap is not in place as the risk of needle stick injury is increased and sterility of the needle may be compromised if packaging is punctured.

Recall of Medicina IV Luer Slip syringe (IVS03) batch number 19040303 (MDA/2019/043). Issued 11 December 2019. Manufactured by Medicina – syringes incorrectly packaged with a needle could mean they are not sterile and could cause a needlestick injury.

Spectra Optia apheresis: anticoagulant bags used with 'Correct Connect' connectors – risk of unbroken 'frangible' connector during use (MDA/2019/041). Issued 4 December 2019. Manufactured by Terumo BCT – inadequately broken anticoagulant 'frangible' may lead to clotting and inadequate therapy during apheresis procedures.

Article citation: Drug Safety Update volume 13, issue 6: January 2020: 5.