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 healthcare professionals that the licence for ingenol mebutate gel (Picato) has been suspended as a precautionary measure while the European Medicines Agency (EMA) continues to investigate concerns about a possible increased risk of skin malignancy. We advise to stop prescribing Picato and to consider other treatment options for actinic keratosis as appropriate.

Second, we inform prescribers of alemtuzumab (Lemtrada) for relapsing multiple sclerosis of the recommendations following a review triggered by serious cardiovascular and immune-mediated adverse reactions. See page 4 for the new indication for Lemtrada, additional contraindications, and strengthened monitoring requirements before, during, and after treatment.

On page 7, we notify healthcare professionals of new educational materials to support the valproate pregnancy prevention programme in female patients using valproate. We also inform of recent amendments made to clinical guidelines to support the regulatory position that valproate should not be used in women and girls of childbearing unless other options are unsuitable and the pregnancy prevention programme is in place.

Next, on page 10, we advise healthcare professionals fitting Nexplanon (etonogestrel) contraceptive implants of a new insertion site to reduce further the rare risk of neurovascular injury and the implant migrating through the vasculature.

On page 12, read about how you can support the MHRA's adverse drug reaction (ADR) awareness week campaign on 17–23 February 2020. The theme is polypharmacy, and we advise healthcare professionals to be especially alert for ADRs in patients taking more than one medicine and to report any suspected ADRs to the Yellow Card Scheme.

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Ingenol mebutate gel (Picato▼): suspension of the licence due to risk of skin malignancy

Stop prescribing Picato and consider other treatment options for actinic keratosis as appropriate. The licence of ingenol mebutate (Picato) has been suspended as a precautionary measure while the European Medicines Agency (EMA) continues to investigate concerns about a possible increased risk of skin malignancy.

Advice for healthcare professionals:

- the licence of ingenol mebutate gel has been suspended as a precautionary measure while the EMA continues to investigate an increased incidence of benign and malignant skin tumours in several clinical studies (see previous Drug Safety Update October 2019)
- stop prescribing ingenol mebutate gel and consider other treatment options for actinic keratosis as appropriate
- existing unexpired stock of ingenol mebutate gel is being recalled from UK pharmacies and wholesalers (see Class 2 Medicines Recall)
- advise patients who have been treated with ingenol mebutate gel to continue to be vigilant for new skin lesions within the treatment area and to seek medical advice immediately should any occur
- report any suspected adverse drug reactions associated with medicines containing ingenol mebutate to the Yellow Card Scheme; reports can still be received for suspended medicines

www.mhra.gov.uk/yellowcard

Review of skin cancer risk

Ingenol mebutate gel (Picato▼) is indicated for the treatment of actinic keratosis in adults when the outer layer of the skin affected is not thickened or raised. It is used as a short course of 150 micrograms/gram gel on the face and scalp for 3 days, or 500 micrograms/gram gel on the trunk and extremities for 2 days.

The potential for ingenol mebutate gel to induce skin cancer was considered during the initial licence application and a 3-year safety study was initiated. In October 2019, we informed healthcare professionals via Drug Safety Update that an in-depth European review of ingenol mebutate gel had started to assess data from several sources showing an increased number of skin cancers with this medicine.

In January 2020, following final results from the 3-year safety study indicating a higher occurrence of skin cancer, the EMA recommended suspending the marketing authorisation (licence) for ingenol mebutate gel as a precaution while the evidence was reviewed, noting that alternative treatments are available.

Study findings

Several studies have found a higher incidence of skin tumours in the treatment area in patients who had used ingenol mebutate gel or a related ester, namely:

- A higher incidence of squamous cell carcinoma with ingenol mebutate gel compared with imiquimod was found in the final results of the 3-year safety study in 484 patients (3.3% versus 0.4% of patients) that was agreed at the time of licensing
- A higher incidence of benign tumours (keratoacanthoma) compared with vehicle was seen in pooled 8-week trials with ingenol mebutate gel in 1262 patients (1.0% versus 0.1% of patients)

- A higher incidence of tumours, including basal cell carcinoma, Bowen's disease and squamous cell carcinoma, was seen compared with vehicle in four clinical trials with ingenol disoxate (an ester related to ingenol mebutate whose clinical development has been stopped) in 1234 patients (7.7% versus 2.9% of patients)

Post-marketing reports of skin tumours in patients treated with ingenol mebutate gel have also been received. Time to onset ranged from weeks to months.

Other studies have not shown an increased tumour incidence with ingenol mebutate gel and there is uncertainty over interpretation of some of the study data. Although a number of uncertainties remain and the data is still being reviewed, given the concerns regarding the possible risk of skin malignancy the EMA has recommended a precautionary EU-wide suspension of Picato. A letter was sent to healthcare professionals to inform them of these measures in January 2020.

Advice to give to patients

Since 2017, the patient information leaflet for Picato has included advice for patients to be vigilant for new lesions in their treatment area. Although the new EMA advice does not require patients to be recalled to discuss the risks, patients who have previously used Picato should be reminded of the need for continued vigilance and to immediately talk to their doctor if they notice any new scaly red patches, open sores, or elevated or warty growths in the treatment area.

Picato is authorised and supplied to allow for a 2 to 3 day treatment course and was recalled from pharmacies and wholesalers in the UK on 27 January 2020. As such, we do not consider it likely that patients will be currently using Picato at the time of publication of this article. However, patients who have been dispensed Picato but not yet used it, or patients who are in the middle of their treatment course, are advised to speak to their prescriber.

UK suspected adverse drug reactions

In the past year, around 34,000 packs of ingenol mebutate gel were dispensed in the UK.[1] Since 2013 and up to January 2020, we have received reports of 10 cases of skin malignancies in the UK associated with ingenol mebutate gel, including cutaneous squamous cell carcinoma (including one metastatic case), atypical fibroxanthoma, neuroendocrine carcinoma of the skin, Bowen's disease, and basosquamous carcinoma. These reports were received in both clinical trial and post-marketing settings.

Article citation: Drug Safety Update volume 13, issue 7: February 2020: 1.

1. Data derived from IQVIA MIDAS Q4 2018 to Q3 2019, by the MHRA, January 2020

Lemtrada▼ (alemtuzumab): updated restrictions and strengthened monitoring requirements following review of serious cardiovascular and immune-mediated reactions

A review of the benefits and risks of alemtuzumab (including fatal reactions) in the treatment of multiple sclerosis has now concluded and recommended a revised indication, additional contraindications, and strengthened monitoring requirements before, during and after treatment.

Patients offered alemtuzumab should be alerted to the early risks of cardiovascular events and thrombocytopenia around the time of infusion and to the delayed risk of immune-mediated reactions. Healthcare professionals should inform patients what to do if they develop any symptoms of these disorders.

Advice for healthcare professionals:

Restricted indication

- alemtuzumab should only be used as single disease-modifying therapy in adults with either:
  - highly active relapsing-remitting multiple sclerosis despite a full and adequate course of treatment with at least one disease-modifying therapy or
  - rapidly evolving severe relapsing-remitting multiple sclerosis defined as 2 or more disabling relapses in 1 year, and with one or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2-lesion load compared to a recent MRI scan

New contraindications and revised monitoring requirements

- alemtuzumab is contraindicated in patients with:
  - severe active infection until complete resolution
  - uncontrolled hypertension
  - a history of arterial dissection of the cervicocephalic arteries
  - a history of stroke
  - a history of angina or myocardial infarction
  - clotting abnormalities including treatment with antiplatelet or anticoagulant therapy
  - autoimmune diseases (apart from multiple sclerosis)
- only administer alemtuzumab in a hospital with ready access to intensive care facilities
- monitor patients closely before, during, and after alemtuzumab infusions for cardiovascular reactions and non-immune thrombocytopenia
- monitor patients for autoimmune disorders for at least 48 months after the last infusion – some autoimmune reactions have been reported after this routine monitoring period

Advice to give to patients

- alert patients receiving alemtuzumab to the signs and symptoms of serious adverse reactions described within a few days of an infusion and to seek urgent medical attention if they develop the following
  - chest pain, coughing up blood, or breathing difficulty
  - drooping of the face, severe headache, neck pain, weakness on one side, or difficulty speaking
  - skin or eyes turning yellow, or dark urine, abdomen pain, bleeding or bruising easily (signs of liver damage)
  - fever, swollen glands, bruising, or rash

Restricted indication and new contraindications for use

Lemtrada (alemtuzumab) is a monoclonal antibody authorised for the treatment of adults with relapsing-remitting multiple sclerosis. In May 2019, we informed of interim restrictions on the use of alemtuzumab (Lemtrada▼) for relapsing multiple sclerosis during an urgent European safety review of serious cardiovascular reactions occurring within a few days of infusion and of immune-mediated events.

The review concluded that serious cardiovascular reactions can rarely occur within 1 to 3 days of alemtuzumab infusions in people without any identifiable risk factors. Reactions included myocardial ischaemia, cerebral haemorrhage, arterial dissection of the cervicocephalic arteries, pulmonary alveolar haemorrhage, and non-immune thrombocytopenia.

The review also found unpredictable and potentially fatal immune-mediated reactions can occur within months and up to at least 4 years after treatment with alemtuzumab. Reactions included autoimmune hepatitis, haemophagocytic lymphohistiocytosis, and acquired haemophilia A. The review also identified serious cases of Epstein-Barr virus reactivation reported after treatment, including hepatitis. Some patients developed more than one autoimmune disorder following treatment.

Alemtuzumab should now only be used in adults with highly active relapsing-remitting multiple sclerosis if they have not responded to a full and adequate course of treatment with another disease-modifying treatment or if they have rapidly evolving severe relapsing-remitting multiple sclerosis. New contraindications and risk minimisation measures have also been introduced and a letter sent to prescribers and dispensers of alemtuzumab.

Frequencies of reactions reported

The frequency of thrombocytopenia (including both immune and acute non-immune cases) associated with alemtuzumab is common (affecting up to 1 in 10 patients). The frequency of myocardial infarction, pulmonary alveolar haemorrhage, and arterial dissection is not known because these reactions were only observed in the post-marketing setting. However, estimated post-marketing reporting indicates that the rate of events occurring within a week of treatment were 2 cases per 10,000 patients for myocardial infarction; 3.6 per 10,000 patients for stroke; 1.6 per 10,000 patients for arterial dissection; and 4.3 per 10,000 patients for pulmonary alveolar haemorrhage.

The frequency of acquired haemophilia A is uncommon (up to 1 in 100 patients) and the frequency of haemophagocytic lymphohistiocytosis is rare (up to 1 in 1000 patients). The frequency of autoimmune hepatitis is not known as this reaction was only observed in the post-marketing settings. The estimated post-marketing reporting rate was 10.7 cases of autoimmune hepatitis per 10,000 patients.

Revised monitoring requirements for alemtuzumab infusions

Alemtuzumab treatment should be started and monitored by a neurologist experienced in the treatment of multiple sclerosis in a hospital with immediate access to specialists and equipment required for the diagnosis and management of adverse reactions, including intensive care facilities.

Before starting alemtuzumab infusions:

- check urinalysis including microscopy; full blood count (with differential white cell count); thyroid function test; serum creatinine and liver function tests;
- take baseline electrocardiogram (ECG) and vital signs including blood pressure and heart rate

During alemtuzumab infusions:

- monitor patients clinically and record their blood pressure and heart rate continuously or at least once every hour
- discontinue the infusion if they develop a severe adverse reaction such as a serious cardiovascular or haemorrhagic event

After completing alemtuzumab infusions:

- monitor patients for infusion reactions for at least 2 hours; consider hospital admission in any patient developing a serious adverse reaction and continue observing them until it has resolved
- discuss the risk of delayed infusion-related reactions with patients and tell them to seek urgent medical care if they experience any possible symptoms or signs
- check platelet counts immediately after finishing treatment on days 3 and 5 of the first infusion course and on day 3 of any subsequent course. Clinically significant thrombocytopenia should be monitored until it resolves and consider referring to a haematologist for advice on management.

Patients should be monitored for early signs of autoimmune disorders until at least 48 months after the last dose of alemtuzumab. Patients should be told that more than one autoimmune disorder could develop and that autoimmune conditions have been reported after this routine monitoring period.

Updated risk management programme

The Lemtrada patient alert card, prescriber checklist and guides for patients and healthcare professionals will be updated with detailed information on the risks of cardiovascular and immune-mediated reactions and the revised monitoring requirements.

Provide the patient guide and alert card to patients before prescribing alemtuzumab and discuss the risks of treatment with them.

Report any suspected adverse drug reactions on a Yellow Card

Healthcare professionals and patients should continue to report any suspected adverse drug reactions to alemtuzumab to the Yellow Card Scheme.

Article citation: Drug Safety Update volume 13, issue 7: February 2020: 2.

Valproate (Epilim▼, Depakote▼) pregnancy prevention programme: updated educational materials

In January 2020, healthcare professionals received updated educational materials to support the valproate pregnancy prevention programme. Valproate is contraindicated in girls and women of childbearing potential, unless the conditions of the pregnancy prevention programme are met.

Advice for healthcare professionals:

- valproate is contraindicated in girls and women of childbearing potential, unless the conditions of the valproate pregnancy prevention programme are met
- changes have been made to the educational materials to support healthcare professionals and female patients; the updates clarify the existing regulatory situation and are not due to new advice
- use the updated educational materials to support the valproate Pregnancy Prevention Programme (dated November 2019):
    - Patient card
    - Patient booklet
    - Booklet for healthcare professionals
    - Annual Risk Acknowledgement Form
- review all girls and women of childbearing potential using valproate medicines to ensure that the conditions of the valproate pregnancy prevention programme, described in the documents, are met
- consult the latest clinical guidance for use of valproate, including recent amendments by NICE on four clinical guidelines to support the regulatory position that valproate should not be used in women and girls of childbearing unless other options are unsuitable and the pregnancy prevention programme is in place

Reminder of requirements

Valproate should not be used in girls and women of childbearing potential unless other treatments are ineffective or not tolerated, as judged by an experienced specialist. Valproate is contraindicated in girls and women of childbearing potential, unless the conditions of the valproate pregnancy prevention programme ('prevent') are met.

Children exposed to valproate in utero are at high risk of serious developmental disorders (in 30– 40% of cases) and of congenital malformations (in approximately 10% of cases). There is no safe dose of valproate that can be used in pregnancy (see Key facts about the risk of valproate in pregnancy).

Evidence from patient surveys suggest that there are still gaps in the implementation of the pregnancy prevention programme, for example women of childbearing potential on valproate medicines who have not been asked to sign the Annual Risk Acknowledgement Form. All girls and women of childbearing potential using valproate medicines should be reviewed at least annually to ensure that the conditions are met.

Changes made to the materials

In January 2020, relevant healthcare professionals were sent by post or Alliance Tote boxes (for pharmacies) a letter and updated educational materials.

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

The most recent materials are all dated as November 2019 for consistency. To order new or further materials, please contact Sanofi medical information department on 0845 372 7101 or email UK-Medicalinformation@sanofi.com .

Booklet for healthcare professionals

Following comments from the MHRA and stakeholders, including healthcare professionals and patient groups, updates were made to the content of the Booklet for healthcare professionals.

The main changes made from the previous version (dated May 2018) are as follows:

- New section: Definition of specialist prescribers (page 6)
- New section “Contraception” (page 7)
- New section “Does ‘prevent’ [the pregnancy prevention programme] apply to my patient?” (page 8)
- Clarification that the provisions apply when a patient is being switched
- from valproate to another treatment (page 12)

The changes were made to clarify the existing regulatory situation and not due to new regulatory measures or advice.

Annual Risk Assessment form

The Annual Risk Assessment form was updated in March 2019 to improve the layout and to clarify when a patient was exempt from the pregnancy prevention plan.

Specialists should comply with guidance given on the form if they consider the patient is not at risk of pregnancy, including the need for regular review in case her risk status changes. If the absence of pregnancy risk may change (for example, the patient is pre-menarchal), the date for the next annual discussion of the risks must be documented and the patient or the patient’s family or caregivers asked to contact the prescriber rapidly if the situation changes.

More information on how to use the Annual Risk Assessment form can be found in the Drug Safety Update, April 2019. The only change made to the form since March 2019 is to update the date for consistency with the other materials.

Patient booklet

The advice in the patient booklet has not changed. Provide the booklet to any female patient who is using valproate for any indication (or their caregiver) and no longer has a copy.

Patient card, pharmacy warning stickers, and dispensary poster

The advice in the pharmacy materials to support the Pregnancy Prevention Programme has not changed. Pharmacy materials are:

- Patient Card: provide a card to all female patients when dispensing valproate medicines. Note: If there is a Patient Card already attached to the box, please detach that copy and give to the patient; Do not stick the dispensing label on top of this card or over the warning on the front of the pack
- Warning Stickers: for use if valproate is dispensed out of its original packaging
- Dispensary A4 poster: for display in the dispensary area to remind pharmacy staff of these requirements.

A statutory patient information leaflet should always be provided with a medicine containing valproate, even if dispensed in a pharmacy box.

NICE: updated clinical guidelines

To support the regulatory position that valproate should not be used in women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years) unless other options are unsuitable and the pregnancy prevention programme is in place, in January 2020 the National Institute for Health and Care Excellence (NICE) amended their clinical guidelines for:

- Epilepsies
- Antenatal and postnatal mental health
- Bipolar disorder
- Depression in adults

The Drug Safety Update, April 2019 links to additional clinical guidance to support healthcare professionals in understanding their clinical responsibilities for valproate.

Monitoring impact

The MHRA continues to monitor trends in the prescribing of sodium valproate to assess the impact of regulatory recommendations and introduction of the pregnancy prevention programme using primary care data from the Clinical Practice Research Datalink GOLD database. For reports, see the MHRA's Valproate in women and girls guidance page.

We will continue to monitor these and other data sources, including clinical audits and patient surveys, and will take action as necessary to protect public health.

Article citation: Drug Safety Update volume 13, issue 7: February 2020: 3.

Nexplanon (etonogestrel) contraceptive implants: new insertion site to reduce rare risk of neurovascular injury and implant migration

Amended advice on the insertion site for Nexplanon contraceptive implants following concerns regarding reports of neurovascular injury and implants migrating to the vasculature (including the pulmonary artery).

Advice for healthcare professionals:

- an implant should be inserted subdermally by a healthcare professional who has been appropriately trained and accredited – correct insertion of the implant just under the skin is essential to reduce the risk of neurovascular injury and the implant migrating through the vasculature
- review the updated guidance for how to correctly insert the implant, including an amended diagram that illustrates:
    - the new insertion site
    - the correct position of the arm for insertion (flexed at the elbow with the woman's hand underneath her head)
    - how to view the needle (by sitting and viewing it from the side) to avoid deep insertion
- show the woman how to locate the implant and advise her to do this occasionally; if she has any concerns, she should return promptly to the clinic for advice
- localise any implant that cannot be palpated (for example, by imaging the arm) and remove it at the earliest opportunity – perform chest imaging if it cannot be located in the arm
- implants inserted at the previous site that can be palpated should not pose a risk and do not need to be moved to the new site; only replace implants if you have concerns regarding their location or if routine replacement is due
- report any suspected side effects to Nexplanon on a Yellow Card, including difficulties with insertion or adverse incidents from migration of the implant or related to its removal

Risk of neurovascular injury and implant migration

Nexplanon is a highly effective, long-acting contraceptive implant containing etonogestrel, a synthetic progestogen. Nexplanon acts by preventing ovulation and is usually effective for 3 years. Safety and efficacy have been established in women between 18 and 40 years of age. For maximum effectiveness and safety, Nexplanon needs to be correctly implanted by someone who is trained to fit it.

There have been reports of neurovascular injury and migration of the contraceptive implant from the insertion site and in rare cases into the pulmonary artery. Some cases have reported haematoma and excessive bruising at the insertion site and dyspnoea.

Although this risk has been known since 2016 (see Drug Safety Update, June 2016), reports continue to be received with Nexplanon. Up to June 2019, the MHRA is aware of 126 reports of implant migration. Of these reports 18 mention migration to the lung, with some mentioning multiple instances of implants that have migrated to the lung.

Worldwide, a total of 107 cases of migration to the pulmonary artery and lung have been identified by the marketing authorisation holder since Nexplanon was launched (between 28 August 1998 to 3 September 2019).

Although no specific risk factors have been identified, potential risk factors include:

- deep insertion
- insertion in an inappropriate site
- insertion in thin arms

Updated advice for insertion of the implant

Following continued receipt of reports, the manufacturer of Nexplanon has further explored the anatomy of the arm to identify an insertion site with the lowest number of vascular/neurological structures. The recommended site for insertion is just under the skin at the inner side of the non-dominant upper arm about 8–10 cm from the medial epicondyle of the humerus and 3–5 cm posterior to the sulcus (groove) between the biceps and triceps muscles. The updated instructions have been added to the product information for Nexplanon and a letter has been sent to healthcare professionals. The Faculty of Sexual and Reproductive Healthcare (FSRH) has also issued a statement.

Subdermal insertion of the implant is the best way to avoid injury, and use of the new site is thought to minimise the risk of migration to the lung and neurovascular injury in case of inadvertent deep insertion. The insertion site is located in an area overlying the triceps muscle, a location generally free of major blood vessels and nerves.

The woman's arm should be flexed at the elbow with her hand underneath her head (or as close as possible) during insertion and removal of the implant. This increased flexion should deflect the ulnar nerve away from the insertion site, potentially further reducing the risk of ulnar nerve injury during implant insertion and removal. On insertion, it is essential to view the needle and tenting of the skin to ensure subdermal insertion.

Evidence from the literature shows that implants found in the vasculature can become endothelised into the pulmonary artery.[1,2,3] If they are located early enough it is possible to remove them by endovascular procedure.[4,5] Women should be shown how to locate the implant immediately following insertion and advised to check the position of the implant occasionally to ensure it has not migrated.

Expert removers' network

There is a network of healthcare professionals who are experienced in implant localisations and difficult removals and who are available for consultation. To request additional information on implant insertion and removal, contact the network by calling 01992 467 272.

Report any suspected adverse reactions on a Yellow Card

Healthcare professionals and patients should continue to report any suspected adverse drug reactions to Nexplanon to the Yellow Card Scheme.

Article citation: Drug Safety Update volume 13, issue 7: February 2020: 4.

1. D'Journo XB, et al. *Ann Thorac Surg* 2015; **99:** 1828.

2. Patel A, et al. *Ann Thorac Surg* 2014; **97:** 1452.

3. O'Brien A, et al. *Ann Thorac Surg* 2015; **2254:** 2255.

4. Heudes P-M, et al. *Case Rep Womens Health* 2015; 8: 6–8.

5. Maroteix P, et al. *Ann Fr Med Urgence* 2015; **5:** 332–33.

Support Yellow Card: report suspected reactions in patients taking multiple medicines

Be especially alert for adverse drug reactions (ADRs) in patients taking more than one medicine and report any suspected ADRs to the Yellow Card Scheme. Show your support for the MHRA's ADR awareness week campaign on 17-23 February 2020 by sharing material on social media and discussing with colleagues and patients the importance of reporting suspected side effects.

What can you do to improve the safe use of medicines?

- don't delay in reporting suspected adverse drug reactions (ADRs) to the Yellow Card Scheme online or via the Yellow Card app (download from the Apple App Store or Google PlayStore)
- when prescribing or reviewing medicines for people with complex or multiple conditions, consider if medicines use is optimised and there is good justification for use of those medicines at the same time
- use the product information for medicines to identify interactions, relevant precautions, and safety monitoring advice
- talk to your colleagues about the importance of monitoring and regularly reviewing people who are taking multiple medicines and discuss with them how reporting suspected ADRs to the Yellow Card Scheme improves the safe use of medicines
- follow us on our social media channels and show your support for the importance of reporting suspected ADRs by retweeting, commenting, liking, and sharing material with your social media contacts using #PatientSafety, #polypharmacy, #yellowcard

Advice you can give to patients, families, and caregivers about medicines safety

- following the instructions in the leaflet that comes with your medicines lowers the risk of some side effects – this includes taking the right dose at the right times and whether to take it with or without food or drinks
- report suspected side effects to the Yellow Card Scheme; even if you have recently stopped a medicine due to a suspected side effect or interaction with other medicines, foods, or herbal products
- if you or a member of your family are using multiple medicines, you can talk to your doctor, nurse, or pharmacist about a medicines review

Patient on multiple medicines? Watch out for interactions and side effects.

The MHRA's adverse drug reaction (ADR) awareness week campaign will be taking place on 17–23 February 2020. This year's theme is the importance of reporting side effects during polypharmacy.

Polypharmacy is the routine use of 4 or more prescription, over-the-counter, or traditional medicines at the same time by a patient. Some polypharmacy, such as in secondary prevention of cardiovascular events, can reduce the risk of future morbidity and mortality in patients. However, polypharmacy can also increase the likelihood of a patient having side effects, as well as increase the risk of interactions between medicines and with foods or herbal products.

Polypharmacy in older people

Polypharmacy is very common, especially in older individuals who are likely to be taking medicines for chronic long-term conditions.[1] In 2017, a study into medication use in older people (65 years and older) in England showed a 4-fold increase in the number of people taking 5 or more medicines (from 12% to 49%).[2] A third of people older than 75 years in England now take at least 6 medicines, and over 1 million people take 8 or more medicines a day.[3]

In addition to older people being more likely to be on multiple medicines, they may also be more susceptible to developing adverse reactions since they may metabolise or excrete medicines less effectively and be more sensitive to their effects. Therefore, it is particularly important to regularly review the need for medicines being taken by older people and to be vigilant for interactions and suspected adverse drug reactions.

1. Cantlay A, et al. InnovAiT 2016; 9: 69–77.

2. Gao L et al. Age and Ageing 2018; 47: 1–6.

3. Health and Social Care Information Centre. Prescriptions dispensed in the community, statistics for England, 2004–2014. Published July 2015. Accessed October 2019.

Information and resources about polypharmacy

Polypharmacy is one of WHO's 3 Global Patient Safety Challenges, which aim to shine a light on particular patient safety issues that pose a significant risk to health.

NICE's Key Therapeutic Topic on Multimorbidity and polypharmacy provides advice on problematic polypharmacy and on optimising a person's medicines to support the management of long-term health conditions.

Other important resources are:

- The Scottish Government Polypharmacy Model of Care Group's 2018 guidance on Polypharmacy, Realistic Prescribing
- Royal Pharmaceutical Society's Polypharmacy: Getting our medicines right
- English Deprescribing Network (EDeN)'s launch briefing

If deprescribing is considered, available resources should be used, including advice in the Summary of Product Characteristics, to ensure safe and effective withdrawal of medicines. This is particularly important for some medicines such as opioids, antidepressant medicines, and corticosteroids, where abrupt discontinuation should be avoided.

How does reporting improve medicines safety?

The MHRA continually reviews the safety of all medicines. Some adverse drug reactions can only be identified when medicines are used for a long time in a wide range of different people, so it is very important that suspected adverse drug reactions are reported to the Yellow Card Scheme.

Every report made by a healthcare professional or a patient or caregiver plays a critical role in understanding the benefits and risks of medicines in clinical use, allowing action to be taken to minimise risks. Reporting helps to improve the safe use of medicines for all patients and, in some cases, can result in better tailored prescribing advice, which can help improve adherence to treatment.

About the Yellow Card Scheme

All healthcare professionals, parents, and caregivers can report any suspected adverse reactions to the Yellow Card Scheme, including to:

- medicines
- vaccines
- blood factors and immunoglobulins
- herbal medicines
- homeopathic remedies

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.

You can also use the app to access the latest safety information from the MHRA about medicines and medical devices on the Newsfeed. Search for medicines to see details of Yellow Card reports others have made. Medicines of interest can also be added to a Watch List to receive news and alerts about new side effects and safety advice as it emerges. We also have dedicated guidance on the Yellow Card Scheme for healthcare professionals including accredited CPD e-learning modules.

The Yellow Card Scheme can also be used to report suspected concerns about medicinal devices, defective medicines, and side effects or safety concerns about e-cigarettes or refill liquids.

Local networks and resources

Healthcare professionals in all settings throughout the UK can contribute to improved medicines safety and awareness reporting of suspected adverse drug reactions. One way to support the safety culture for your organisation is to engage with key networks and resources available locally.

The UK's 5 regional Yellow Card Centres work with healthcare professionals, patients and organisations to promote the Yellow Card Scheme and the importance of reporting reactions. Your local Yellow Card Centre can help you or your organisation to raise awareness of the Yellow Card Scheme.

- Northern and Yorkshire Yellow Card Centre
- North West England Yellow Card Centre
- West Midlands Yellow Card Centre
- Scotland: Yellow Card Centre Scotland
- Wales: Yellow Card Centre Wales

In England, you can also engage with your local Medication Safety Officer (MSO). The MSO of your NHS trust, CCG, or community pharmacy helps to support healthcare professionals in reporting suspected adverse drug reactions to the Yellow Card Scheme and medication errors via local reporting mechanisms. MSOs also work as a group to identify local and national trends in safety reporting, share best practice for new medicines risk advice, and support other medication safety champions in local committees, networks, and groups.

About the campaign

The reporting of suspected adverse drug reactions is key to patient safety. This campaign builds on the past award-winning campaigns to help encourage greater local and national awareness about the importance of reporting to support the earlier detection of safety issues.

Campaign material freely available for reuse includes a general animation about reporting and infographics. Material is also available on the Yellow Card website.

The MHRA's ADR campaign follows on from international MedSafetyWeek in November 2019, which the MHRA and Uppsala Monitoring Centre coordinate.

Article citation: Drug Safety Update volume 13, issue 7: February 2019: 5.

Letters and drug alerts sent to healthcare professionals in January 2020

Letters from January 2020

- Methotrexate for autoimmune diseases: recommendations to reduce potentially fatal dosing errors
- Modafinil: potential risk of congenital malformations during pregnancy
- Ecalta 100mg (anidulafungin): Solution for infusion must no longer be frozen
- Lemtrada▼ (alemtuzumab): Restricted indication, additional contraindications and risk minimisation measures
- Nexplanon (etonogestrel 68 mg, implant for subdermal use): update to the insertion and removal instructions to minimise the risks of neurovascular injury and implant migration
- ▼Picato (ingenol mebutate) – Suspension of the marketing authorisation due to risk of skin malignancy
- Valproate (Epilim▼, Depakote▼): Pregnancy Prevention Programme – revised educational materials
    - 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 January 2020, the MHRA sent a letter asking healthcare professionals to be vigilant for and report any adverse reactions associated with e-cigarettes or vaping (see Drug Safety Update from January 2020).

Drug alerts from January 2020

Class 4 Medicines Defect Information: Dr. Reddy's Laboratories (UK) Ltd, Finasteride 5 mg Tablets, PL 08553/0261 (EL (20)A/03). Issued 29 January 2020. The Patient Information Leaflet (PIL) provided with the batches listed in the alert is missing warning and precautions documented in the Summary of Product Characteristics regarding the risk of mood alterations and depression. Ensure that patients are aware of any missing information in the leaflet and understand the need to seek medical advice in cases of psychiatric symptoms.

Class 4 Medicines Defect Information: Advanz Pharma Zapain 30mg/500mg Tablets (Codeine Phosphate /Paracetamol), PL12762/0034, (EL(20)A/01). Issued 14 January 2020. Pharmacies should be aware of a discrepancy on the product packaging for the batches listed in the alert. The discrepancy relates to “capsules” printed at the top right of the packs in error, instead of tablets.

In January 2020, a Class 2 Medicines Recall was also issued for Picato gel ▼.

Article citation: Drug Safety Update volume 13, issue 7: February 2020: 6.

Medical Device Alerts issued in January 2020

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.

Convex two-piece skin barriers (Natura /Surfit/Combihesive Wafers) for use with ostomy bags – recall due to risk of stoma injury, bleeding and leakage under the skin barrier (MDA/2020/002). Issued 16 January 2020. Manufactured by ConvaTec – specific batches of convex two-piece skin barriers have been incorrectly manufactured with off-centre starter/stoma hole. The alert advises to share this information with all those who may also have affected product, including patients, to identify and arrange for return of affected devices.

Professional use defibrillator/monitor: all HeartStart XL+ (Model number 861290) - risk of failure to deliver therapy (MDA/2020/003). Issued 28 January 2020. Manufactured by Philips – due to hardware or software issues the device may fail to start, unexpectedly restart or deliver defibrillation therapy at the wrong energy level. The alert advises following the recommended actions of two recent Field Safety Notices and, if possible, have ready access to a backup defibrillator until the corrective actions have been undertaken.

Notice regarding patients using phenindione

Healthcare professionals may also wish to be aware of a recent notice from Siemens Healthcare following reports of falsely depressed creatinine results for patients on phenindione therapy when using the enzymatic methodology of the ADVIA assay. The instructions for use (IFU) for the ADVIA Chemistry ECRE_2 assay will be updated to indicate that use of this assay is not recommended for patients undergoing treatment with phenindione, due to the potential for falsely depressed results.

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