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 you of new restrictions to use and strengthened monitoring requirements for alemtuzumab (Lemtrada) in patients with multiple sclerosis while an urgent EU safety review evaluates reports of serious cardiovascular events and immune-mediated reactions, including autoimmune hepatitis (page 2).

Second, we communicate new restrictions for the 10 mg twice-daily dose of tofacitinib (Xeljanz▼) following study observations of an increased risk of pulmonary embolism and overall mortality with this dose in rheumatoid arthritis (page 5). While an in-depth review of these risks is ongoing, the 10 mg twice-daily dose of tofacitinib, authorised for ulcerative colitis, must not be prescribed in patients at high risk for pulmonary embolism. Patients receiving tofacitinib, irrespective of indication, should be monitored for the signs and symptoms of pulmonary embolism and made aware of the need to seek immediate medical attention if they occur.

Next, we make you aware of the potential risks of skeletal adverse events and biochemical disturbances in neonates exposed to magnesium sulfate in utero following maternal treatment for longer than 5–7 days (page 6).

Finally, we share serious concerns about a recent fall in reporting of suspected adverse drug reactions to the Yellow Card Scheme from key healthcare professional groups, including GPs, pharmacists, and hospital doctors (page 8). Every Yellow Card report counts – don't delay, report today!

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Lemtrada (alemtuzumab) and serious cardiovascular and immune-mediated adverse reactions: new restrictions to use and strengthened monitoring requirements

While an urgent EU safety review evaluates reports of serious cardiovascular events and immune-mediated reactions, including autoimmune hepatitis, the use of alemtuzumab (Lemtrada) has been restricted and strengthened requirements have been introduced to monitor vital signs and liver function before and during treatment. All patients on alemtuzumab for multiple sclerosis should be alerted to these risks and what to do if symptoms occur.

Advice for healthcare professionals:

Restricted indication for new patients

- alemtuzumab for multiple sclerosis should only be started in adults with either:
  - relapsing-remitting multiple sclerosis that is highly active despite an adequate course of treatment with at least 2 other disease-modifying therapies
  - highly active relapsing-remitting multiple sclerosis if all other disease-modifying therapies are contraindicated or otherwise unsuitable
- patients already on alemtuzumab for multiple sclerosis may continue treatment if it is beneficial and they have discussed the additional monitoring requirements and new risks with their prescriber

New monitoring requirements and precautions for use

- monitor vital signs, including blood pressure, before and periodically during alemtuzumab infusion – consider stopping the infusion and conducting additional monitoring, including electrocardiography (ECG), if any clinically significant changes in vital signs occur
- monitor liver function tests before and during treatment with alemtuzumab for multiple sclerosis
- consider discontinuing treatment in patients who develop hepatic injury or serious immune-mediated reactions
- evaluate immediately any patients who develop early manifestations of pathologic immune activation, and consider a diagnosis of haemophagocytic lymphohistiocytosis (see below)

Advice to give to patients

- alert patients to the symptoms of:
  - pulmonary haemorrhage, myocardial infarction, stroke, and arterial dissection within days of infusion – patients should seek urgent medical attention if they develop any symptoms of these disorders (see below), which may occur within a few days of treatment
  - hepatic injury – patients should seek urgent medical help if they develop any symptoms of liver injury including abdominal pain, jaundice, dark urine, and unexplained nausea or vomiting
  - haemophagocytic lymphohistiocytosis – patients should seek immediate medical attention if they develop unexplained fever, lymphadenopathy, bruising or rash, including if these symptoms occur several years after treatment
- patients should speak to their doctor if they have any questions about alemtuzumab for multiple sclerosis

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New urgent safety review following reports of serious cardiovascular and immune-mediated adverse reactions

An urgent EU-wide review of the safety of alemtuzumab for multiple sclerosis has begun following reports of immune-mediated reactions and serious cardiovascular events, particularly within 3 days of dosing. There have been some life-threatening and fatal cases.

While the review is ongoing, the use of alemtuzumab for multiple sclerosis has been restricted and new monitoring requirements introduced. We will update healthcare professionals once final recommendations are available.

Worldwide, more than 34,000 people with multiple sclerosis have been treated with Lemtrada in clinical trials and post-marketing in clinical practice. Since alemtuzumab (Lemtrada) was marketed in the UK in 2014, an estimated 9371 patient-courses have been administered (9474 patient-years).[1]

1. Data derived from IQVIA IMS MIDAS, 01/2014-12/2018, and analysed by the MHRA, April 2019. The patient-courses estimate is based on the assumption that the average duration of a patient-course was 4 days. The patient-years estimate is based on the WHO Defined Daily Dose (DDD) of 0.13mg.

Cases of cardiovascular reactions

The underlying mechanism for these cardiovascular reactions has not been determined.

Pulmonary haemorrhage

5 patients developed pulmonary alveolar haemorrhage within a day of their last infusion of alemtuzumab. Reported symptoms or signs included cough, haemoptysis, hypoxia, and dyspnoea. These post-marketing cases did not have any confounding factors.

Myocardial infarction

10 post-marketing cases of myocardial infarction with increased troponin levels have been reported within 48 hours of last infusion. Of these cases, 5 did not have any risk factors, and for 2 cases it is difficult to establish the role of alemtuzumab due to other possible causes.

Arterial dissection

6 post-marketing cases of vertebral and/or carotid artery dissection have been reported, 4 of which occurred within 3 days of last infusion of alemtuzumab. No risk factors for arterial dissection were present in 3 patients.

Stroke

13 patients experienced stroke (haemorrhagic in 11 cases; ischaemic in 2) within a day of last infusion. A case series of 5 of these patients with no risk factors was published recently.[2] Some patients had significant increases in their blood pressure during treatment with alemtuzumab.

2. Azevedo CJ, et al. *Lancet Neurol* 2019; 18: 329–31.

Cases of immune-mediated disorders

The immune-mediated reactions described below generally occurred around 6 months after alemtuzumab exposure so may represent secondary autoimmune mechanisms.

3. Canham LJW, et al. *ECTRIMS* 2017; 199783

4. El Sankari S, et al. *Acta Neurol Belg* 2018; 118: 331–33.

Autoimmune hepatitis

Several post-marketing cases of autoimmune hepatitis, including 2 fatalities have been reported following alemtuzumab. 2 of these cases have been published.[3,4]

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Haemophagocytic lymphohistiocytosis

7 cases have been reported of secondary haemophagocytic lymphohistiocytosis within a few months to 4 years of starting treatment. These events occurred during post-marketing use of the medicine. A causal relationship could not be excluded in 6 cases and a description of 2 of these cases has been published.[5]

5. Saarela M, et al. *Neurology* 2018; 90:849-51.

Secondary haemophagocytic lymphohistiocytosis is a life-threatening syndrome of uncontrolled immune activation. Clinical criteria for the diagnosis of secondary haemophagocytic lymphohistiocytosis have been established by the Histiocyte Society.[6]

6. Henter J-I, et al. *Pediatr Blood Cancer* 2006; 48: 124–31.
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About Lemtrada (alemtuzumab)

Lemtrada (alemtuzumab) 12 mg concentrate for solution for infusion was authorised in the EU in September 2013 for the treatment of adults with remitting relapsing multiple sclerosis and active disease defined by clinical or imaging features. Lemtrada is a monoclonal antibody that binds to CD52.

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.

Further information

Direct Healthcare Professional Communication. Alemtuzumab (Lemtrada): Restriction of use due to serious safety Concerns. April 2019.

EMA announcement. Use of multiple sclerosis medicine Lemtrada restricted while EMA review is ongoing. 12 April 2019

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Tofacitinib (Xeljanz▼): restriction of 10 mg twice-daily dose in patients at high risk of pulmonary embolism while safety review is ongoing

Following observation in a clinical study of an increased risk of pulmonary embolism and overall mortality with tofacitinib 10 mg twice-daily in rheumatoid arthritis, a safety review has started and new contraindications introduced. The 10 mg twice-daily dose of tofacitinib (authorised for ulcerative colitis) must not be used in patients at high risk of pulmonary embolism.

New safety review and restrictions

A European safety review of tofacitinib (Xeljanz▼) has begun following results from an ongoing study (study A3921133) in patients with rheumatoid arthritis aged 50 years and older with at least one cardiovascular risk factor. The findings show an increased risk of pulmonary embolism and overall mortality, compared with a TNF inhibitor, when patients were treated with 10 mg of tofacitinib twice-daily (twice the recommended dose for rheumatoid arthritis of 5 mg twice-daily).

For more information on the measures, see EMA press release.

Since the 10 mg twice-daily dose is recommended for the initial treatment (for up to 16 weeks) in ulcerative colitis, until the review has concluded, patients with ulcerative colitis at high risk of pulmonary embolism should not start treatment with tofacitinib. Patients who are already being treated with the 10 mg twice-daily dose of tofacitinib who are at high risk of pulmonary embolism should be switched to alternative treatments.

While an in-depth review of these risks is ongoing, the 10 mg twice-daily dose of tofacitinib must not be prescribed in patients with one or more of the following risk factors for pulmonary embolism:

- Use of combined hormonal contraceptives or hormone replacement therapy
- Heart failure
- Previous venous thromboembolism, either deep venous thrombosis or pulmonary embolism
- Inherited coagulation disorder
- Malignancy
- Patients undergoing major surgery

Additionally, other risk factors for pulmonary embolism to be considered when prescribing tofacitinib 10 mg twice-daily are age, obesity (BMI>30 kg/m^2), smoking, and immobilisation.

Background

The start of this safety review follows interim advice in March 2019 for prescribers to adhere to the authorised dose of 5 mg twice-daily for the treatment of rheumatoid arthritis and psoriatic arthritis (letter to healthcare professionals). We will communicate more information on these measures and further advice as it arises. A letter is being sent to healthcare professionals to inform of the temporary recommendations.

For information for patients, see EMA website

Patients receiving tofacitinib, irrespective of indication, should be monitored for the signs and symptoms of pulmonary embolism, and be advised to seek medical attention immediately if they experience them.

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Magnesium sulfate: risk of skeletal adverse effects in the neonate following prolonged or repeated use in pregnancy

Maternal administration of magnesium sulfate for longer than 5–7 days in pregnancy has been associated with skeletal adverse effects and hypocalcaemia and hypermagnesemia in neonates. If use of magnesium sulfate in pregnancy is prolonged or repeated, consider monitoring of neonates for abnormal calcium and magnesium levels and skeletal adverse effects.

Advice for healthcare professionals:

- maternal administration of magnesium sulfate for longer than 5–7 days in pregnancy may be associated with adverse effects in the foetus, including hypocalcaemia, skeletal demineralisation, osteopenia, and other skeletal adverse effects
- if prolonged or repeated use of magnesium sulfate occurs during pregnancy (for example, multiple courses or use for more than 24 hours), consider monitoring of neonates for abnormal calcium and magnesium levels and skeletal adverse effects
- report suspected adverse drug reactions to magnesium sulfate following exposure during pregnancy on a Yellow Card

Background

Magnesium sulfate is authorised for the prevention of further seizures associated with eclampsia in pregnancy and for the treatment of magnesium deficiency in hypomagnesemia.

The NICE guideline Preterm labour and birth (NG25) advises offering intravenous magnesium sulfate for foetal neuroprotection in women in preterm labour or having a planned preterm birth within 24 hours, who are between 24 weeks and 29 weeks and 6 days of pregnancy. The guideline also advises considering use in women in preterm labour or having a preterm birth between 30 weeks and 33 weeks and 6 days of pregnancy.

The dose recommended by NICE, if given for a full 24 hours, equates to 28 grams of magnesium sulfate, equivalent to usual minimum dose in eclampsia – see Summary of Product Characteristics for full details. However, the new advice should be considered in case uncertainty around exact timing of delivery results in repeat administration.

Previous safety concerns about prolonged use of magnesium sulfate in pregnancy

In 2013 the US FDA issued a safety communication recommending against use of magnesium sulfate for more than 5–7 days when used as a tocolytic (not an authorised indication in the UK). Such prolonged exposure may result in significantly higher cumulative doses than those encountered with use of magnesium sulfate in the UK for eclampsia or foetal neuroprotection (see FDA data summary for description of doses and period of use associated with reports).

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The US FDA alert was based on 4 reports of fractures and 35 reports of osteopenia or radiographical bone abnormalities in neonates, some of which also describe hypocalcaemia and hypermagnesemia in the neonate. The long-term clinical significance of the biochemical and skeletal effects is unknown, with the available evidence suggesting a transient effect.

Although overall, most clinically relevant cases were seen following high doses of magnesium sulfate over prolonged periods, we are aware of reports in the literature of electrolyte imbalances in the neonate following lower doses or after treatment periods of less than 5 days (for example, clinically significant hypocalcaemia in a neonate following cumulative administration of an estimated 100 grams of magnesium sulfate).[1]

1. Bodenmann P, et al. *Nephrol Ther* 2014, 10: 51–57.

National review of risk in prolonged use

The MHRA is not aware of any reports in the UK of skeletal adverse effects or relevant biochemical effects in the neonate following use of magnesium sulfate for foetal neuroprotection. However, following efforts to achieve increased uptake in preterm labour and birth (including through the PReCePT project), data suggests usage is increasing in the UK. Healthcare professionals should therefore be vigilant for any adverse effects in the neonatal period if in-utero exposure to magnesium sulfate is prolonged.

The Commission on Human Medicines and its Expert Advisory Groups the Medicines for Women's Health Expert Advisory Group and the Paediatric Medicines Expert Advisory Group considered data for the use of magnesium sulfate in the UK. Based on their recommendations, the product information for products containing magnesium sulfate will be updated to warn of skeletal adverse effects observed with administration for more than 5–7 days in pregnancy.

Healthcare professionals are advised to consider monitoring neonates for abnormal calcium and magnesium levels and skeletal adverse effects if maternal treatment with magnesium sulfate is prolonged or repeated beyond current recommendations.

Report suspected adverse drug reactions in pregnancy

Please continue to report any suspected adverse drug reactions via the Yellow Card Scheme. Remember only a suspicion is needed to report – if in doubt, please complete a Yellow Card. For more about the importance of reporting suspected adverse drug reactions associated with medicines in pregnancy, see Drug Safety Update July 2018.

Healthcare professionals, patients, and caregivers can report suspected side effects via the Yellow Card website or via the Yellow Card App. Download the app today 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. The App is also piloting additional questions on medicine use during pregnancy – download the app and try it out for yourself.

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Yellow Card: please help to reverse the decline in reporting of suspected adverse drug reactions

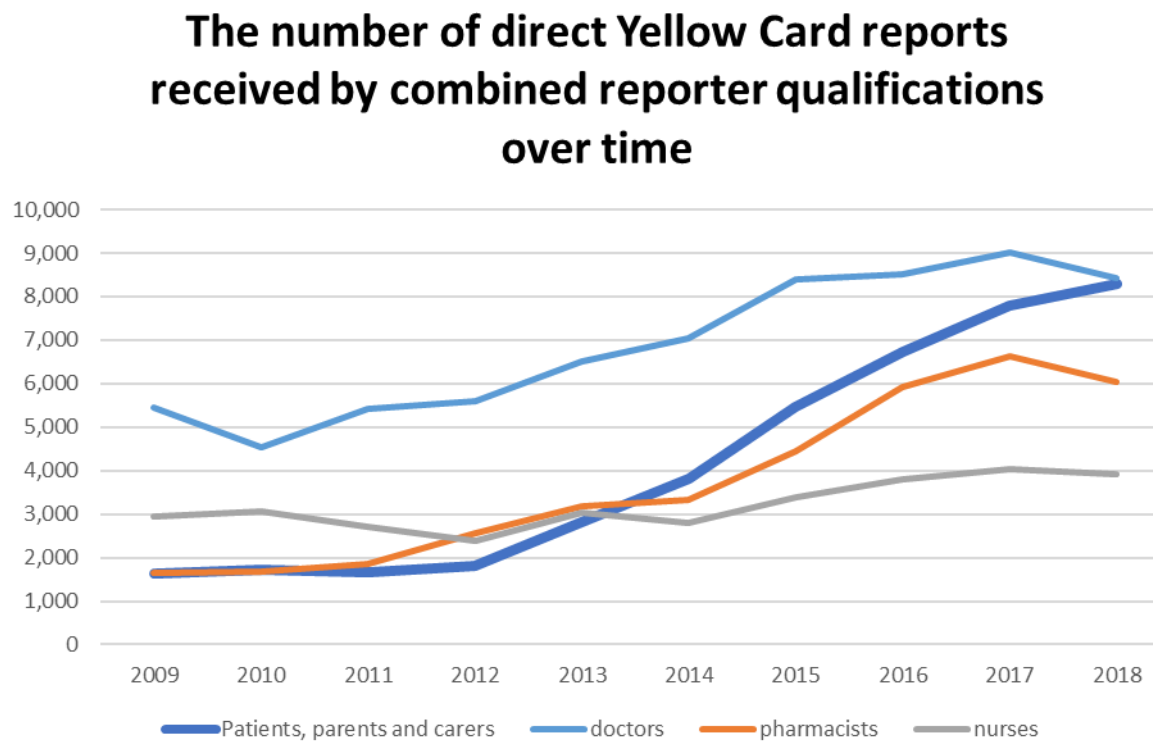
2018 saw a fall in reporting of suspected adverse drug reactions (ADRs) to the Yellow Card Scheme from key reporter groups, including GPs, pharmacists, and hospital doctors. Every Yellow Card report counts, and a few minutes taken by you or your patient to report can make a lifetime of difference for others – don't delay, report today!

Decrease in reporting in 2018

Reporting suspected adverse drug reactions (also termed ADRs) to the Yellow Card Scheme helps the MHRA to monitor the safety of medicines and improve patient safety.

Between 2009 and 2017, the number of reports we received from UK healthcare professionals doubled. However, in 2018, there was a significant decrease in reports from some healthcare professional groups.

Figure 1 shows how reports from you and your colleagues have changed over time.



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In 2018, a decrease in reports was seen in the following groups, which are self-designated when a reporter submits a Yellow Card:

Healthcare professional group	Decrease in number of reports	Decrease in 2018 compared with 2017
Hospital pharmacists	-380	-11%
General practitioners (GPs)	-280	-4%
Community pharmacists	-226	-14%
Hospital doctors	-161	-7%
Physicians	-142	-46%
Nurses	-122	-5%
Healthcare professionals in hospitals	-53	-7%

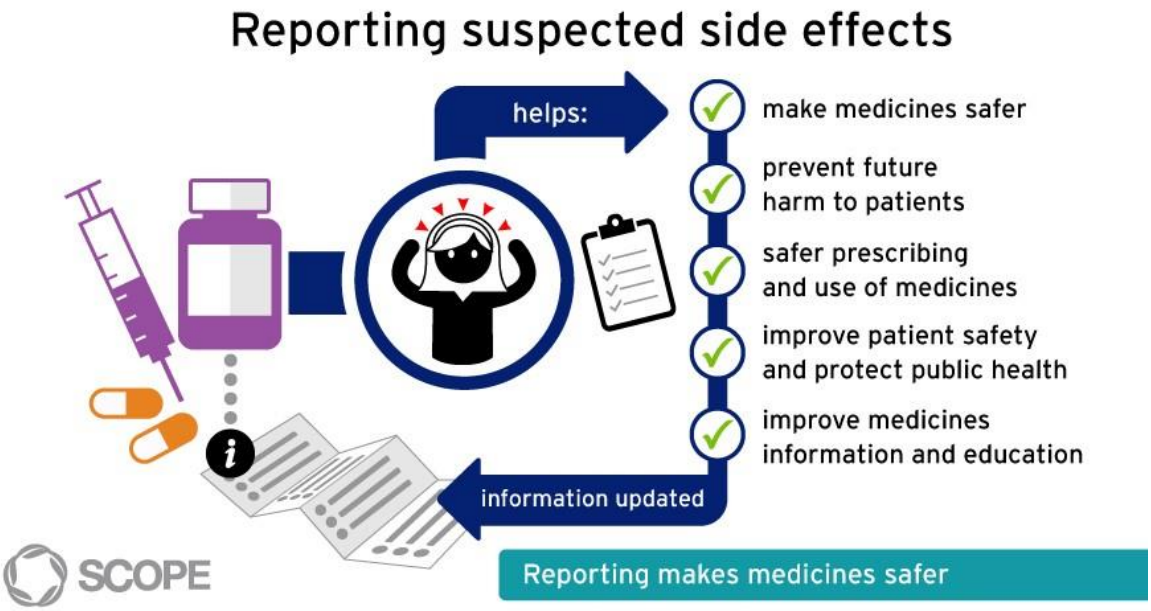
Reporting improves medicines safety

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 has a vital role in understanding the benefits and risks of medicines in clinical use, allowing action to be taken to minimise risks.

Reporting results in better tailored prescribing advice, which can help improve adherence to treatment and minimise the risk of avoidable harm. The value of the Scheme has been demonstrated many times and has helped identify numerous safety issues.

Figure 2: How your report makes medicines safer



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What should I report?
The effectiveness of the Yellow Card Scheme to detect new drug safety signals is dependent upon your reporting of your suspicions and observations.

Yellow Cards can be used for reporting suspected adverse drug reactions to medicines, vaccines, herbal or complementary products, whether for self-medication or prescribed. This includes suspected adverse drug reactions associated with misuse, overdose, or medication errors, or from use of unlicensed and off-label medicines.

What should I report?
You should report all suspected adverse drug reactions that are:

- serious, medically significant, result in harm, associated with medication errors where harm occurs. Serious events are fatal, life-threatening, a congenital abnormality, disabling or incapacitating, or resulting in hospitalisation
- associated with newer drugs and vaccines (▼); irrespective of whether they are serious or not; the most up-to-date list of black triangle medicines is available on the MHRA website.

If in doubt whether to report or not, please complete a Yellow Card.

How can I complete a Yellow Card?
You can report:

- online at www.mhra.gov.uk/yellowcard
- via the Yellow Card app available in the Apple App Store or Google Play Store
- through SystmOne, Vision, and MiDatabank clinical IT systems
- by emailing yellowcard@mhra.gov.uk or by downloading printable forms from the Yellow Card website and sending them freepost to 'Yellow Card'
- by completing Yellow Card forms in the BNF, NPF, MIMS, or PAGB OTC directory
- by calling the Yellow Card reporting line on 0808 100 3352.

You can also report Yellow Cards for all medicines, medical device adverse incidents, defective medicines, counterfeit or fake medicines or medical devices, and safety concerns with e-cigarettes or their refill containers on the Yellow Card website.

Remember it is good practice if you have completed a Yellow Card to inform your patient that you have done so and discuss with them how reporting contributes to improving the safe use of medicines.

Don't wait for someone else to report it
It is estimated that only 10% of serious reactions and between 2 and 4% of non-serious reactions are reported. Under-reporting coupled with a decline in reporting makes it especially important to report all suspicions of adverse drug reactions to the Yellow Card Scheme.

Please complete a Yellow Card even if you think someone else may have reported one – the system can detect duplicate reports and we can use information to add to details about the case.

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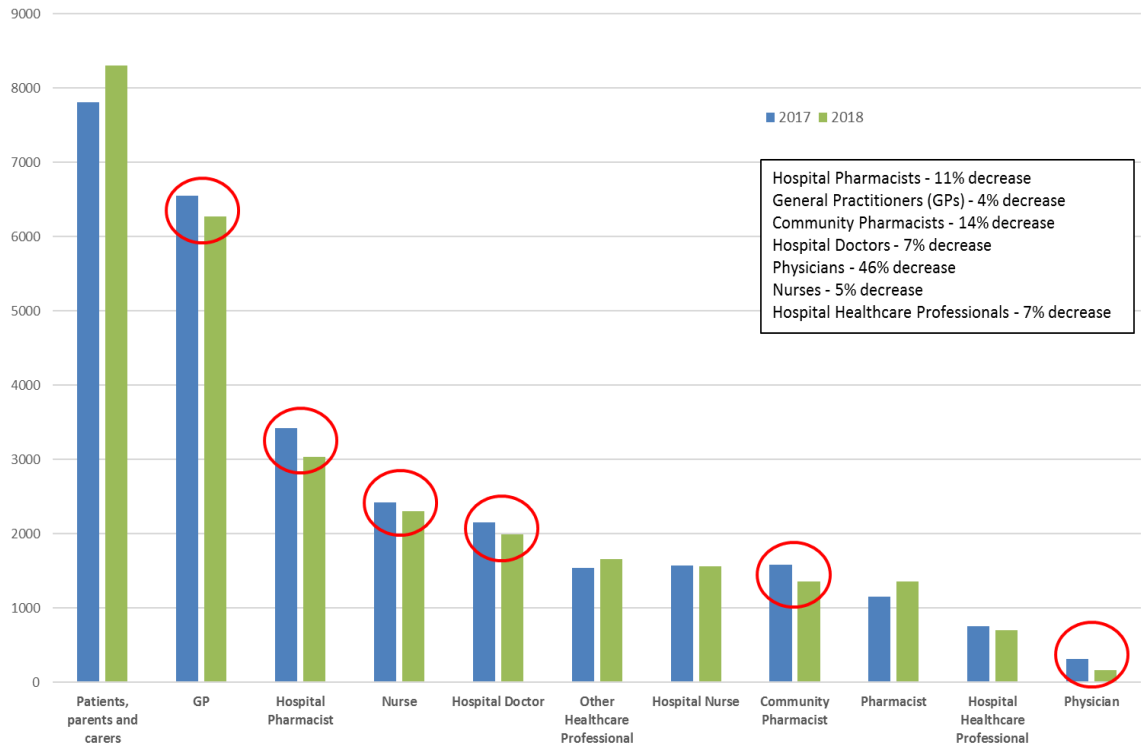
What can healthcare professionals and their organisations do to raise awareness of the Yellow Card Scheme?

- Download our animation and add it to the screens in your patients' waiting area
- Encourage dialogue regularly between your colleagues and patients, parents, and caregivers about the importance of reporting suspected adverse drug reactions to the Yellow Card Scheme and new Drug Safety Updates
- Discuss suspected adverse drug reactions that you have reported and how you've kept up to date with emerging safety issues with Drug Safety Update in your professional revalidation, annual appraisals and for continuing professional development (CPD) purposes
- Engage locally with your regional Yellow Card Centre or your local Medication Safety Officer (MSO) in England at your hospital trust
- See the dedicated guidance on the Yellow Card Scheme for healthcare professionals including accredited CPD e-learning modules and downloadable materials to share on social media
- Want to add the Yellow Card logo to supporting information on your website, intranet, e-mail signatures or screensavers? Get in touch with us.

Talking to your patients about side effects and the Yellow Card Scheme

Patient reports, including those from parents and carers, now account for the highest reporting group compared to any specific group of healthcare professionals, for example compared to GPs or hospital pharmacists (see figure 3 for a comparison).

Figure 3: Direct reports received by the MHRA in 2017 and 2018, with decreases shown with red circles



'Other healthcare professionals': The most frequently reported professions within this group were other healthcare professionals (51%), pharmacy assistants (16%), radiographers (12%), and pre-registration pharmacists (11%). They also include dentists, optometrists, coroners, healthcare assistants, paramedics, chiropodists, medical students, and other non-specified health professionals.

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Next time you are talking to your patients or even producing or providing health information for patients, remember to mention the potential for side effects and how to report them to the Yellow Card Scheme.

Providing and discussing the Patient Information Leaflet that accompanies all licensed medicines forms an ideal basis for this discussion.

Every report counts, and a few minutes taken by you or your patient to report can make a lifetime of difference for others. Don't delay, report today.

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Letters and drug alerts sent to healthcare professionals in April 2019

Letters

- Alemtuzumab (Lemtrada): Restriction of use due to serious safety concerns
- Selenase (sodium selenite pentahydrate): similarity of oral and parenteral preparations; risk of dispensing errors
- Erelzi▼ (etanercept) 25 mg and 50 mg pre-filled syringes: limited number of batches with French syringe labels

Drug alerts

- Class 4 Medicines Defect Information: Zoledronic acid 5mg solution for infusion (MDR 51-03/19). Issued 4 April 2019. Some packs from the listed batch contain the wrong Patient Information Leaflet. When dispensing, please check the Patient Information Leaflet and replace if needed.
- Company led drug alert - Nutriflex Omega Special 2500ml PL 03551/0118. Issued 8 April 2019. Batches are being recalled as ongoing stability studies have identified that they may have an out-of-specification result in the glucose chamber at the end of shelf-life.
- Class 4 Medicines Defect Information: Chloramphenicol 0.5% W/V Antibiotic Eye Drops (MDR 105-03/19). Issued 9 April 2019. Braille is missing from the carton and the packs contain the Patient Information Leaflet (PIL) for the product with legal status 'POM'.
- Class 4 Medicines Defect Information: Ativan 4mg/1ml Solution for injection (MDR 57-04/19). Issued 24 April 2019. The product description on the carton was changed from 10 x 1ml ampoules to 10 x 2 ml ampoules. The updated text reflects the size of the ampoules, which is 2 ml. The concentration and total volume of the ampoules has not changed and remains 4 mg lorazepam in 1 ml of solution.
- Class 4 Medicines Defect Information: Prednisolone 5mg Tablets (MDR 61-04/19). Issued 26 April 2019. An error on the braille means that the strength reads as 1 mg instead of 5 mg.

For the latest alerts, including those from May 2019 on Macopharma intravenous infusion bags and Co-amoxiclav Power for Oral Suspension, see Alerts and recalls for drugs and medical devices.

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Medical Device Alerts issued in April 2019

In this monthly update, we highlight selected Medical Device Alerts that have been issued recently by MHRA. Please note, this is not an exhaustive list of medical device alerts. For all Medical Device Alerts from MHRA, see Alerts and recalls for drugs and medical devices.

- Hoists: Molift Mover 180/205 mobile hoist and Molift Air ceiling hoist - all sizes of 2-point sling bars – risk of fracture of hooks in use (MDA/2019/020). Issued 1 May 2019. Manufactured by Etac and supplied in UK by R82 UK Ltd – if the hooks connecting the spreader bar to the hoist break during use, the patient could fall.

Article citation: Drug Safety Update volume 12, issue 10: May 2019: 6.

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