Contribution of Yellow Cards to identifying safety issues

It is easy to report suspected side effects, known as adverse drug reactions, on the Yellow Card website: www.mhra.gov.uk/yellowcard or via the Yellow Card app. Download the app via iTunes Yellow Card for iOS devices or via PlayStore Yellow Card for Android devices.

Stay up to date with the latest emerging safety advice on medicines by subscribing to the MHRA's monthly bulletin called Drug Safety Update: www.gov.uk/drug-safety-update

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.

The value of the Yellow Card Scheme has been demonstrated many times and it has helped to identify numerous important safety issues, many of which were not recognised as being related to a particular medicine until we received information on Yellow Cards. After the table of safety issues there are some detailed case study examples.

Contents

Table of safety issues to which Yellow Cards have contributed to

The following table shows some of the safety issues which Yellow Card reports have contributed to in the assessment of, or helped to identify:

Year	Medicine	Adverse Reaction	Resulting action or advice
January 2019	Labetalol	Nipple pain	Patient information leaflet strengthened to reflect nipple manifestations of Raynaud's phenomenon.
September 2018	Rivaroxaban (Xarelto ▼)	Drug administration error: Patients taking rivaroxaban on an empty stomach and developing thromboembolic events	Patient information leaflet updated to re-order information in section 3 to increase clarity and drug safety update article published about the risks of taking the medicine on an empty stomach.
August 2018	Propranolol	Abnormal weight gain	Strengthened product information with the addition of 'abnormal weight gain' to the undesirable effects section.
June 2018	Sertraline	Maculopathy	Safety issue raised with the EMA (as product has a mutual recognition licence) who concluded that the product information should be strengthened to include 'maculopathy' in the undesirable effects section.
May 2018	Fluconazole and citalopram	Drug interaction: Reported cases of serotonin syndrome and serious cardiovascular effects	Safety issue raised with the EMA (as product has a mutual recognition licence) who concluded that the product information should be strengthened to include an interaction between fluconazole and citalopram and resulting serotonin syndrome and cardiovascular effects risks.
May 2018	Umeclidinium (Anoro ▼)	Dizziness	Strengthened product information with the addition of 'dizziness' to the undesirable effects section.

April 2018	Lamotrigine	Hypogammaglobulinaemia	Strengthened product information with the addition of 'hypogammaglobulinaemia' to the undesirable effects section.
January 2018	Aripiprazole	Oculogyric crisis	Strengthened product information with the addition of 'oculogyric crisis' to the undesirable effects section.
December 2017	Perindopril	Raynaud's phenomenon	Safety issue raised with the EMA (as product has a mutual recognition licence) who concluded that the product information should be strengthened to include Raynaud's phenomenon.
October 2017	Varenicline	Loss of consciousness	Safety issue raised with the EMA (as product is centrally authorised) who concluded that the product information should be strengthened to include transient loss of consciousness, including a warning about the effects on driving and using machines whilst taking varenicline.
July 2017	Cetalkonium chloride and choline salicylate (Bonjela)	Swollen tongue	Strengthened product information with the addition of 'hypersensitivity' reactions to the undesirable effects section.
May 2017	Tiotropium bromide (Braltus)	Choking	Instructions for use updated and drug safety update article published.
September 2014	Novorapid (insulin aspart)	No ADR – packaging complaint (formation of air bubbles in solution)	Centrally authorised product – referred to EMA.
September 2014	Denosumab	Osteonecrosis of the jaw; monitoring for hypocalcaemia	Reminder on precautions and updated recommendations for the need of a dental examination and appropriate preventive dentistry before treatment.

June and September 2014	Ferumoxytol	Serious hypersensitivity reactions	New recommendations to minimize risk including contraindication for patients with drug allergies and changes in the method of administration.
July 2014	Fentanyl patches	Life threatening harm from accidental exposure	Reminder of potential for life-threatening harm from accidental exposure from swallowing or transfer to other individuals, particularly in children.
June 2014	Chlorhexidine	Risk of chemical burns	Highlighted risk to premature infants and initiated EU review.
May 2014	Voriconazole	liver toxicity, phototoxicity, and squamous cell carcinoma	Reminder on risk of liver toxicity, phototoxicity, and squamous cell carcinoma and the importance of liver function testing and avoiding exposure to sunlight.
April 2014	TNF-alpha inhibitors	Risk of tuberculosis	Precautions to be vigilant for infectious diseases: conduct pretreatment screening and close monitoring during treatment.
March 2014	St John's wort and hormonal contraceptives medicines and implants	Interaction resulting in reduced contraceptive effect	Reminder about herbal products that contain St John's wort and the interaction with hormonal contraceptives.
January 2014	Capecitabine	Risk of severe skin reactions	Discontinue treatment if severe skin reactions occur. Reminder to inform patients of possible severe skin reactions. Reminder advice on Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) reactions.
January 2014	Temozolomide[o]	Hepatic injury and failure	Updated warnings and monitoring guidance.
December 2013	Recombinant interferon-beta	Thrombotic microangiopathy	Healthcare professionals are advised to be vigilant for symptoms and signs of complications.

November 2013	Risperidone and paliperidone	Intraoperative floppy iris syndrome (IFIS) detected during cataract surgery	Product information for risperidone and paliperidone updated to include warnings about IFIS.
September 2013	Filgrastim and pegfilgrastim	Life-threatening capillary leak syndrome (CLS)	Precaution to monitor patients and healthy donors for signs and symptoms of CLS and give standard symptomatic treatment immediately if symptoms occur.

Information on the nature of risk (harms) and benefit to healthcare professionals and patients helps allow informed choices to be made about treatment options and in the management of ADRs should they occur.

Patients and health professionals reporting suspected adverse drug reactions to the Yellow Card Scheme help contribute to these important processes. Suspected reactions can be reported online at www.mhra.gov.uk/yellowcard or via the free Yellow Card app.

Gaviscon Infant and constipation

A 3-month-old baby boy was prescribed Gaviscon Infant (containing sodium alginate and magnesium alginate) to manage reflux, a condition in which the contents of the stomach come back up into the food pipe. This can be painful and can damage the gullet. Two days after starting the medicine, the baby experienced severe constipation. As there was no mention of constipation in the Patient Information Leaflet (PIL), the mother contacted their GP who advised to stop the medication and increase water intake. The baby was also given Infacol and miconazole as additional medicines without problems. The baby did not have any relevant medical history of constipation or any other conditions.

Although the mother was not certain that Gaviscon Infant had caused constipation in her baby, she rightly completed a Yellow Card report online as she suspected it might have been the cause.

This child's report alarmed MHRA experts during routine assessment and a more thorough review was conducted. The review identified 6 additional reports of constipation with Gaviscon Infant in children. Four of these cases were reported by parents, one case was reported by a hospital pharmacist, and one case by a nurse. All cases reported Gaviscon Infant as the only suspect drug. In one case, Gaviscon Infant was stopped, and the child recovered but when the medicine was reintroduced, the child experienced the same side effects. Four cases were recovering or had recovered at the time of reporting upon the withdrawal of the drug. None of the patients had any relevant past medical history suggestive of constipation or any medications that might increase the risk of constipation.

Following thorough assessment by the MHRA specialist unit who look at medicine use in children, it was decided that there is a possible causal association between Gaviscon Infant

and constipation. Gaviscon is soluble in water and has the property to thicken solutions, and so stomach contents and potentially intestinal content, resulting in constipation.

As the product information indicates the medicine is for children aged 1–2 years, it was then agreed to contact the pharmaceutical company to request a full review of all cases highlighting the age of patients who experienced constipation. The ages of the patients varied between 2 weeks to 9 months, except for one child who was a 1-year-old. Therefore, it appears that in these cases the product had been used by a healthcare professional in an unapproved patient age group.

Based on the information received from the pharmaceutical company and the available Yellow Card reports, it was decided to take regulatory action to strengthen the product information with the relevant warnings and precautions.

- Parents and carers know their child best. If you have a suspicion that a side effect might have been caused by a medicine, speak to a healthcare professional. You can report any suspected side effects yourself about your child directly to the MHRA via the Yellow Card Scheme reporting website.

- Always read the Product Information Leaflet (PIL) supplied with medicines for a list of recognised side effects.

- It is important to discuss side effects or any concerns about medicines with your GP, pharmacist or healthcare professional and seek advice.

- Reporting via the Yellow Card Scheme helps identify issues and increases patient safety in children even when a medicine is prescribed outside its licensed indication.

Yasmin and hair loss (alopecia)

After three months of being prescribed Yasmin for oral contraception, a female in her twenties suffered substantial hair loss (alopecia). She suspected this might be due to the medicine she was taking so she checked the Patient Information Leaflet (PIL) inside the packaging of her medicine, as advised to by her pharmacist when she collected her medicine - there was no mention of hair loss under the possible side effects section. She decided to go into her local community pharmacy.

Her pharmacist advised her to make an appointment with her GP but at the same time also had an important discussion with her about side effects and medicines. The pharmacist asked her if she was taking any other medicines at the time – this enabled the possibility of a potential interaction between Yasmin and any other medicines to be ruled out. The pharmacist also asked her if she any of her family members had hair loss, which they did; however, she also mentioned that she had never had any history of hair loss herself.

Even though the pharmacist was not certain that Yasmin was responsible for causing hair loss, they encouraged her to complete a Yellow Card - as only a suspicion that a side effect is occurring because of a medicine is needed to complete a Yellow Card. So she went online and

completed a report.

Through routine assessment by MHRA experts, her Yellow Card report triggered a more thorough review of this issue. This identified a further 14 similar reports for patients ranging from 18 to 37 years old – 7 of which were received directly from patients. At the time of the review, most cases of hair loss were recovered or recovering. The review resulted in the Patient Information Leaflet (PIL) being updated to include hair loss (alopecia) under 'uncommon side effects': out of every 1,000 women who use Yasmin between 1 and 10 may be affected.

- Patient reporting via the Yellow Card Scheme adds value to medicines safety.
- Pharmacists and GPs have a key role to play in promoting patient safety about side effects.
- Check the PIL supplied with your medicine which lists all recognised side effects and interactions.
- Anyone can report suspected side effects: www.mhra.gov.uk/yellowcard
- If you are concerned about a side effect, ask your doctor or pharmacist for advice

Natalizumab (Tysabri▼): importance of early detection of progressive multifocal leukoencephalopathy

Natalizumab is a disease-modifying therapy for adults with multiple sclerosis who have high disease activity despite treatment with beta-interferon, or who have rapidly evolving severe relapsing-remitting disease. Natalizumab is associated with a risk of progressive multifocal leukoencephalopathy (PML). PML is a rare, progressive disease that damages the protective covering (myelin sheath) of nerve fibres, impairing the conduction of signals in the affected nerves in the brain. This disease of the central nervous system can lead to severe disability or death. It is caused by activation of John Cunningham virus (JCV), which usually remains latent and typically causes PML in immunocompromised patients only.

Up to 30 March 2016, MHRA received 36 Yellow Card reports of PML in patients receiving natalizumab, of which 3 were received directly via the Yellow Card Scheme (from healthcare professionals and patients), and 33 indirectly reported from pharmaceutical industry (companies are legally obliged to collect, and report suspected side effects reported to them about their medicines). Of the 33 reports, 17 originated from healthcare professionals, 12 from physicians (speciality unspecified), 2 from hospital doctors, and 2 from non-healthcare professionals. As a newer drug, natalizumab was under additional monitoring (▼), meaning any suspected side effects should have been reported.

Evidence from these reports and several other studies led to new clinical advice to reduce the risk of PML. The information identified cases where there were no noticeable symptoms of

PML but PML was diagnosed through MRI scans and positive JCV DNA in the cerebrospinal fluid. Analysis of these cases suggested that earlier detection of PML was associated with improved outcomes for patients.

Following UK and European review, new advice on screening was issued to clinicians to support risk stratification, aid early detection of PML, and minimise potential risk to patients.

- Report all suspected side effects to medicines under additional monitoring (▼) directly using the online Yellow Card reporting form or the app.
- Yellow Card reporting helps the MHRA to identify and refine the understanding of existing risk factors that may affect the clinical management of patients, leading to better outcomes for patients.

Posaconazole tablets and oral suspension are not interchangeable

Posaconazole is an antifungal medication for the treatment and prevention of fungal infections. The medicine is available as an oral suspension and as tablets.

A patient in hospital was prescribed the oral suspension of posaconazole but was instead given tablets. The oral suspension and tablet are in different forms and contain a different amount of medicine; they are therefore not interchangeable. This medication error resulted in the patient receiving an overdose of posaconazole, developing kidney problems and a headache.

When the hospital pharmacist identified this issue, they contacted the pharmaceutical company that makes the medicine. The pharmaceutical company sent the report to MHRA because they are legally obliged to report suspected side effects.

Similarly, other Yellow Card reports were sent in by other hospital pharmacists from different locations about instances where the posaconazole tablets and oral suspension were directly substituted, resulting in patients not receiving enough posaconazole and developing infections.

MHRA requested a review by the pharmaceutical company of all available global safety data. This was reviewed alongside all Yellow Cards and other safety information. After a UK and European review, it was agreed that it was important to communicate with healthcare professionals to increase awareness of this issue and to prevent patients receiving incorrect dosages of posaconazole.

In addition, other measures were taken to strengthen warnings on the labelling of posaconazole products to state clearly that the oral suspension cannot be directly substituted for the tablet or vice versa at the same dose. The outer packaging of the oral suspension and tablets were also changed to prevent confusion between the tablets and the oral suspension.

To raise awareness among healthcare professionals, MHRA agreed for a letter from the

pharmaceutical company to be sent to healthcare professionals about the safety concern. MHRA also published a Drug Safety Update article highlighting the issue and advice to healthcare professionals.

- If you come across a suspected a suspected side effect occurring in a patient, it is likely you are not alone – don't dismiss it, report it to the Yellow Card Scheme.
- The Yellow Card Scheme receives reports from all over the UK – reporting helps to provide a clearer picture about the safe use of medicines to protect public health.
- If you suspect that your medication is not working as it should it's important to speak to your healthcare professional and report it to the Yellow Card Scheme.
- Healthcare professionals play an important role in being vigilant about suspected side effects and should report them directly to the Yellow Card Scheme.

Nexplanon (etonogestrel) contraceptive implants: reports of device in lung

Nexplanon is a highly effective, long-acting contraceptive that is inserted under the skin of a woman's upper arm. The implant steadily releases the hormone progestogen into the bloodstream, which prevents the release of an egg each month (ovulation). It also thickens the cervical mucus, which makes it more difficult for sperm to move through the cervix and thins the lining of the womb so a fertilised egg is less likely to implant itself. To be effective, Nexplanon needs to be correctly implanted by someone who is trained to fit it.

The MHRA received 3 Yellow Card reports from doctors describing cases in which the Nexplanon implants reached the lung via the pulmonary artery. No definitive set of adverse reactions were associated with these events. However, in some cases, dyspnoea (difficult or laboured breathing), haematoma (solid swelling of clotted blood) at the insertion site, and excessive bleeding at the insertion site were reported. Potential risk factors included deep insertion, insertion in an inappropriate site, or being underweight.

This issue was communicated via the MHRA's Drug Safety Update bulletin and letters were sent out to healthcare professionals from the pharmaceutical company to inform them of this potential risk.

Advice for healthcare professionals included that the implant should only be inserted by healthcare professionals who had been trained and accredited. Extra information was provided on carefully inserting the implant. The advice also recommended the healthcare professional verify the presence of the implant immediately after it was inserted and show the patient how to check it was in the right place, including to check its position frequently for the first few months. If the implant could not be examined by touch upon insertion, healthcare professionals

were advised, as soon as medically appropriate, to perform chest imaging and surgery or endovascular procedures.

- The Yellow Card Scheme can also be used to detect new events
- Stay up to date with the latest emerging safety advice on medicines by subscribing to MHRA's monthly bulletin Drug Safety Update.

Drug interaction between dexamethasone and ritonavir, increased risk of systemic adrenal effects

Corticosteriods are anti-inflammatory medicines used to treat a range of conditions (some examples include dexamethasone, prednisolone, and methylprednisolone). Ritonavir is used to control HIV infection in combination with other drugs.

A hospital pharmacist reported a Yellow Card raising his concerns over the lack of knowledge and warnings relating to the interaction between ritonavir and corticosteroids, particularly during topical corticosteroids (applied directly to the body). The report concerns a young adolescent male who was on long-term anti-retroviral therapy (ART) with a boosted protease inhibitor regimen (darunavir 800 mg/ritonavir 100 mg once a day). He was seen in an acute ophthalmology unit for keratoconjunctivitis, which is the inflammation of the cornea and conjunctiva. He was prescribed dexamethasone eye drops to be taken every 2 hours. Within a short period, he was completely adrenally suppressed with Cushing's syndrome —an extremely complex hormonal condition caused by an excess of cortisol hormone that involves many areas of the body; symptoms include facial swelling/puffiness and weight gain. The hospital pharmacist stated that due to few alternative treatments for keratoconjunctivitis, the ART regimen was changed to allow dexamethasone to be continued and the patient recovered. The reporter felt warnings about interactions may need to be clearer, particularly for dexamethasone because there aren't many alternative treatment options for keratoconjunctivitis and therefore HIV medications may need to be changed.

MHRA received an additional UK case of an interaction between dexamethasone and ritonavir reported by a pharmaceutical company. This case also involved topical dexamethasone and described resulting Cushingoid reactions.

A routine EU review of all available safety information examined these reports. MHRA experts agreed with the pharmacist's concerns in the Yellow Card. The mechanism of this interaction was thought to be linked to an important protein found mainly in the liver and in the intestine that helps to break down and remove toxins and medicines from the body (CYP3A4 inhibitors). As a result, MHRA took regulatory action to ensure the product information was strengthened. Information was added about potential side effects, including the interaction between ophthalmic dexamethasone and ritonavir, to highlight that Cushing's syndrome and/or adrenal suppression may occur after intensive or long-term therapy in predisposed patients, including children. It was advised that treatment should be progressively reduced, not discontinued abruptly. MHRA also published a Drug Safety Update article to communicate advice from the

product information and raise awareness among healthcare professionals.

- Pharmacists and GPs have a key role in promoting patient safety; reporting side effects, including drug interactions which might not be known before, helps the safer use of medicines.

- Remember some medicines can interact with other medicine(s) – always read the product information.

- Keep up to date with emerging medicines safety information by subscribing to MHRA's monthly bulletin Drug Safety Update.

- Patients should always read the patient information leaflet supplied with their medicines. It lists all recognised side effects and interactions; it also advises what to do.

Cobicistat (Stribild▼) and fluticasone: drug interaction

Cobicistat is an antiretroviral medicine used for the treatment of HIV. Fluticasone is a synthetic corticosteroid that is used in the treatment of a variety of inflammatory and allergic conditions.

A man in his thirties was taking a combination treatment containing cobicistat (Stribild▼) for HIV therapy, prescribed by a genitourinary medicine (GUM) clinic. He then started taking a fluticasone inhaler, which was prescribed and dispensed at his GP surgery. Subsequently, the patient developed serious side effects known to be associated with fluticasone. His GP suspected that these side effects might be due to an interaction between the 2 drugs, since the Stribild product information included a warning that use of these medicines together is not recommended. His GP completed a Yellow Card report highlighting this drug interaction and prescribing error.

Cobicistat acts by blocking a protein responsible for breaking down many medicines, including fluticasone and other corticosteroids. Therefore, taking both drugs at the same time can increase the amount of fluticasone in the body, since less of the drug can be broken down. Increased amounts of fluticasone may then cause patients to experience side effects associated with corticosteroids, some of which are serious. For example, Cushing's syndrome can occur when steroid levels are too high, and this can cause thinning of bones and eye problems, such as cataracts.

Routine assessment of this Yellow Card by MHRA experts lead to a review of the product information for both cobicistat and fluticasone. The MHRA received 3 other reports (all received indirectly from pharmaceutical companies) of a suspected interaction between these 2 drugs; all of which resulted in similar side effects with a total of 8 cases in EU. Although a possible interaction was already listed in the Stribild product information and use with fluticasone was not recommended, this warning did not specifically mention the severity of the side effects that may occur. In addition, the warning only included fluticasone and did not mention other corticosteroids, which are likely to have the same effect. There was also no

warning of a possible interaction in the fluticasone product information or other corticosteroid product information. As demonstrated by the case described in this Yellow Card report, there is a possibility that the 2 drugs may not be prescribed or dispensed by the same person. Therefore, the warning at the time was considered insufficient.

Following review at a national and European level, it was agreed to strengthen the warning in the cobicistat product information and to add a warning to the product information for all non-topical corticosteroids about the possibility of an interaction and the types of side effects that may occur. In addition, a Drug Safety Update article was published to communicate this safety issue.

- Report all suspected reactions with products that display a ▼, which indicate it is under additional monitoring – see www.mhra.gov.uk/blacktriangle
- The reporting of medication errors where harm occurs to the Yellow Card Scheme associated with how a medicine is used or prescribed can highlight important patient safety issues.
- Remember, medicines can interact with other medicine(s), foods, and drinks.
- Check the Patient Information Leaflet supplied with your medicine, which lists all recognised side effects and interactions; it also advises you what to do.
- If you are concerned about a side effect or think that the side effect you are experiencing might be due to an interaction, ask your doctor or pharmacist for advice.

Warfarin and calciphylaxis

A detailed review was triggered following the receipt of an alarming Yellow Card report of calciphylaxis (gathering of calcium in blood vessels) in woman in her fifties taking warfarin, an anticoagulant medicine used to reduce the clotting ability of the blood, often referred to as a ‘blood thinner’. Calciphylaxis is a very rare but serious syndrome that involves the deposition of calcium and phosphate in blood vessels and other tissues of the body, resulting in wounds that do not heal. Although it is usually seen in patients with severe chronic kidney disease, it may also occur in the absence of kidney failure. Calciphylaxis may have serious consequences if not treated appropriately.

The lady had a medical history of obesity, irregular heart rate, thyroid deficiency, type 2 diabetes mellitus and raised blood pressure, and was receiving various medications. The patient had undergone a procedure via the right groin called radiofrequency ablation to correct her irregular heart rate. The patient soon started to complain about bleeding spots beneath the skin (ecchymosis), skin death (necrosis), and hard lumps (induration) to both the groin and lower abdomen, with lower abdominal pain. She was referred to a plastic surgery team and warfarin was discontinued. She had extensive dead skin and underwent many surgical procedures to remove the dead skin and repeated skin grafts from healthy parts of her body. Samples taken from the patient showed open skin sores (epidermal ulceration) and calcium

gathering in her arteries (focal medial calcification of the arteries), which indicate calciphylaxis. The patient was transferred for treatment with sodium thiosulphate. One month later, test results confirmed the persistence of calciphylaxis. The patient was discharged 8 months after the initial admission.

The MHRA had 3 additional Yellow Card reports, 2 of which have been reported by hospital doctors. Due to the rare nature of this condition, poor awareness of its existence, and the high usage of warfarin, an extensive search for strong evidence and review was carried out at a national level and also involved EU review. Regulatory action was taken to add new warnings about the possibility that, on rare occasions, warfarin use might lead to calciphylaxis. This was communicated to healthcare professionals via a Drug Safety Update article.

- It is important to talk to your doctor, pharmacist, or nurse if you are worried about your treatment.
- If you have any concerns that the drug you are using is causing you side effects, you can report directly to the MHRA using the online Yellow Card reporting form.
- Healthcare professionals play an important role in increasing patient safety both through directly reporting suspected adverse drug reactions to the MHRA and encouraging patients to report their side effects.
- Reporting helps add further clinical information about the safety profile of established medicines.

Sayana (medroxyprogesterone) and injection site atrophy

A woman in her thirties developed a deep hole in her leg at the site of where Sayana (medroxyprogesterone) was injected for contraception. Previously she had used Depo-Provera for contraception without experiencing any issues. She did not have any medical conditions or allergies and was not overweight. As she was very concerned and did not receive any warnings, she decided to submit a Yellow Card report online.

Through routine assessment at the MHRA, her Yellow Card triggered a further investigation of all reports on the Yellow Card database with similar suspected side effects. There were 21 UK cases of suspected muscle loss (atrophy) at the injection site suspected to be associated with medroxyprogesterone. 17 of which were reported directly to the Yellow Card Scheme - 12 from GPs, 3 from nurses, and 1 by a patient. There were 5 additional reports reported by GPs and other healthcare professionals indirectly to the pharmaceutical company.

In 3 reports, the side effect occurred on the same day as the drug start date. Two cases reported that the side effect occurred 10 and 12 weeks following the first use of the contraception injection. Other cases reported longer side effect start date of 21, 25 and 58 weeks. None of the patients had any relevant past medical history that could increase the risk of injection site atrophy apart from one case where the patient had muscle atrophy (loss) in the past.

Based on all the safety information available, MHRA contacted the pharmaceutical company to ask them to provide a global review of all cases concerning Sayana and injection site reactions. An additional 94 cases of subcutaneous (injected under the skin) medroxyprogesterone reported events indicative of injection-site atrophy were identified. Most cases reported the site of injection as the thigh/leg or abdomen. Four cases reported self-injection, 3 cases reported that the patient received the injection at a clinic or doctor's office, 2 cases reported that a nurse/nurse assistant administered the injection, and in 1 case the injection was administered by a gynaecologist. In 23 cases, it was reported that the side effect occurred after the first injection of subcutaneous medroxyprogesterone.

123 relevant cases of intramuscular (injected into muscles) medroxyprogesterone were identified. The site of injection was reported as the thigh/leg or buttock followed by the arm in most of the intramuscular medroxyprogesterone cases. Four of these cases reported that the injection site atrophy was confirmed via diagnostic procedures such as echography or magnetic resonance imaging (MRI). In 4 cases, it was reported that the patient was either planning to or had received cosmetic treatment for the event or had consulted a plastic surgeon. In 12 cases it was reported that the event occurred after the first or second injection, and in 10 cases it was reported that the event occurred within 6 months of the patient receiving an injection.

Based on the persistent nature of the reaction, regulatory action was taken to add information and warnings to the product information to include injection-site reactions, such as pain/tenderness, nodule/lump, persistent atrophy/indentation/dimpling, and lipodystrophy (where the body is unable to produce fat).

- Always discuss side effects with your healthcare professional.
- Your report matters. Reporting suspected side effects directly to the Yellow Card Scheme helps the safer use of medicines and improved patient safety.
- Always read the product information for recognised side effects and for advice on what to do.
- Even if you are unsure whether a medicine has caused a certain side effects, you can report it – only a suspicion is needed to submit a Yellow Card.

Amlodipine and grapefruit interaction

A male patient in his sixties who drank grapefruit juice three times a day whilst taking a particular brand of amlodipine, prescribed for high blood pressure (hypertension), reported severe swelling to his legs and feet. The swelling resolved when he stopped drinking grapefruit juice.

Routine assessment of this patient's Yellow Card by MHRA experts, lead to a review of the product information for that brand of amlodipine. The MHRA received three other reports of a suspected interaction with grapefruit, all of which provided convincing /strong evidence for an interaction. The review resulted in a strengthening of interaction warnings in the Patient

Information Leaflet (PIL).

It is already known that grapefruit contains a group of chemicals, furanocoumarins, which can affect drug metabolism – the amount of time it takes for a medicine to be broken down by the body. These chemicals inhibit an enzyme that breaks down some medicines, and so this can cause a higher level of the "active" medicine to be present in the body than was intended with the given dose. This can then trigger unpleasant, and sometimes serious, side effects.

Amlodipine belongs to a class of medicines known as calcium channel blockers that lower blood pressure by relaxing the muscles that make up the walls of your arteries.

Other common medicines that are known to interact with grapefruit or grapefruit juice include:

- statins such as simvastatin and atorvastatin
- some calcium channel blockers such as felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine and verapamil. Grapefruit does not affect diltiazem.
- immunosuppressants such as clislosporin, sirolimus, tacrolimus
- entocort which contains budesonide for Crohn's disease
- some medicines used in the treatment of cancers such as crizotinib, lapatinib, linotinib, pazopanib, sunitinib and everolimus
- aliskiren which is used to treat high blood pressure

If you eat grapefruit or drink grapefruit juice and are concerned that it may be interacting with another of your medicines, check the Patient Information Leaflet supplied with the medicine - this lists the known interactions and side effects of a medicine and advises you what to do. If you are still unsure, check with your doctor or pharmacist before drinking grapefruit juice.

- Remember some medicines can interact with other medicine(s), food and drink
- Check the PIL supplied with your medicine which lists all recognised side effects and interactions; it also advises you what to do.
- Anyone is able to report suspected side effects: www.mhra.gov.uk/yellowcard
- If you are concerned about a side effect, ask your doctor or pharmacist for advice

Warfarin and Cranberry juice interaction

Through routine assessment of Yellow Card reports by MHRA experts in 2003, five Yellow Cards suggested an interaction of cranberry juice with warfarin. One report was of a man on warfarin who died six weeks after drinking cranberry juice daily.

Warfarin is an anticoagulant given to patients to prevent the formation of blood clots that can lead to serious and sometimes life-threatening conditions such as a stroke or a heart attack. The interaction with cranberry juice led to an increase in the time taken for his blood to clot, as

measured by International Normalised Ratio (INR) levels. Since the INR levels of patients on warfarin can vary it is critical that INR measurements are closely monitored.

Cranberry juice contains various antioxidants including flavinoids, which are known to inhibit the activity of an enzyme used to metabolise warfarin - cytochrome CYP2C9.

Following publicity from a published report, further Yellow Card reports were received and the MHRA conducted a review of the 12 reports of suspected interaction between warfarin and cranberry juice. Eight involved increases in INR and/or bleeding episodes, in three cases the INR was unstable and in one case the INR decreased. On review of these cases it was concluded that there was sufficient evidence of an interaction between warfarin and cranberry juice for formal advice to be issued. It was not possible to define a safe quantity or brand of cranberry juice, therefore patients taking warfarin are advised to avoid this drink unless the health benefits from the juice are considered to outweigh the risks from any change in INR and bleeding time.

MHRA advised that increased medical supervision and INR monitoring should be considered for any patient taking warfarin and having a regular intake of cranberry juice.

Similar caution should be observed with other cranberry products, such as capsules or concentrates, which might also interact with warfarin. Product information for warfarin products was updated to reflect this new advice and a warning was issued to health professionals that patients taking warfarin should limit or avoid drinking cranberry juice.

- Remember medicines can interact with other medicine(s), food and drink.
- Check the PIL supplied with your medicine which lists all recognised side effects and interactions; it also advises you what to do.
- Report suspected side effects: www.mhra.gov.uk/yellowcard
- If you are concerned about a side effect, ask your doctor or pharmacist for advice

Phenytoin and Purple Glove Syndrome (for pharmacists)

A female patient in her sixties was taking phenytoin injections for treatment of a serious epileptic condition. She developed redness and swelling in her right arm after 15-20 injections were administered at different sites and so went to speak to her local pharmacist. This was later diagnosed as purple glove syndrome - a rare condition where there is discolouration, build-up of fluid in tissue which can result in swelling, and blister formation on the hand. The swelling can lead to localised tissue death due to impaired blood supply and this can sometimes lead to disability. The pharmacist referred the patient for urgent medical treatment but also reported this to the pharmaceutical company that manufactured the medicine. The company sent the report to the MHRA because they are legally obliged to do so.

Through routine assessment by MHRA experts, this report was assessed alongside 3 other UK

reports that were derived from cases reported in the medical literature and 17 other ADR reports from other countries. Following review of this issue the MHRA requested the pharmaceutical company to conduct a worldwide review of their own safety data. This analysis resulted in the addition of purple glove syndrome and warnings under possible side effects of the phenytoin product information. Although the frequency of getting purple glove syndrome is unknown; in most cases, the condition is temporary, and treatment is symptomatic and supportive; reduce oedema and improved limb perfusion while monitoring for progressing vascular compromise and compartment syndrome.

- Pharmacists and GPs are in a unique position to identify and report suspected adverse drug reactions – they have a key role to play in promoting patient safety about side effects with the public.

- All serious reactions should be reported to the MHRA, but if you are not sure whether to report, send a Yellow Card anyway.

- Remember - it's quicker to report directly to the MHRA via the Yellow Card Scheme: www.mhra.gov.uk/yellowcard

Ranitidine and breast disorders (doctors)

A hospital doctor completed a Yellow Card report about a female infant suffering from recurrent episodes of bleeding from both nipples for one day every few months whilst on ranitidine for symptomatic relief of heartburn, indigestion, acid indigestion and hyperacidity. The doctor noted there was no obvious cause for this and suspected it may be related to ranitidine since it is already known to cause abnormal enlargement of male breasts (gynaecomastia).

Another Yellow Card was submitted by a GP concerning a man that experienced sore bleeding nipples which recovered upon discontinuation of ranitidine. At the time, the summary of product characteristics (SPC) – the health professional equivalent to the Patient information Leaflet (PIL) - listed 'breast symptoms in men'.

Through routine assessment by MHRA experts, these two Yellow Card reports submitted by doctors triggered a review of suspected reports of nipple disorders and gynaecomastia as the warnings at the time were considered insufficient. This ultimately resulted in new wording and strengthening of existing warnings within the updated product information to include breast symptoms and breast conditions (such as gynaecomastia and galactorrhoea – spontaneous flow of milk from breasts unassociated with childbirth or nursing). The Patient Information Leaflet was also updated to include the side effects of 'breast tenderness and or breast enlargement, breast discharge'.

- Doctors are considered the cornerstone of reporting suspected ADRs to the Yellow Card Scheme – in 2017, nearly 40% of all direct healthcare professional Yellow Card reports were received directly from doctors.

- GPs have an important role to play in promoting patient safety, both through reporting suspected adverse drug reactions directly as well as by informing patients how to report themselves and where to find information on suspected side effects.

- Don't delay report today: www.mhra.gov.uk/yellowcard

Varenicline (Champix▼) and somnambulism (sleep walking)

A doctor reported a case of a male patient who woke up in a police cell. The patient thought he was dreaming as he had previously experienced vivid dreams. The police officer told the man he would be breathalysed as he had fallen asleep at the wheel of his car on the side of the road. Within his report, the doctor stated that the patient had no history of psychiatric problems and no medication other than varenicline (to help him stop smoking), drugs or alcohol had been consumed by the man. The doctor suspected that this episode may have been caused by taking varenicline and so reported it to the pharmaceutical company that manufactures the medicine. The company sent the report to the MHRA because they are legally obliged to do so.

Through routine assessment by MHRA experts, this report was assessed alongside 14 other Yellow Card reports and 12 ADR reports from other countries. They contained similar suspected reactions associated with sleep walking, dreaming and nightmares. At the time, the UK product information listed abnormal dreams, insomnia and circadian rhythm sleep disorder but this was considered to be insufficient. The MHRA requested the pharmaceutical company to conduct a worldwide review of safety data. Following UK and European review, it was agreed that it was important for patients to be aware that varenicline could make them walk in their sleep with unknown frequency and a new warning of ‘sleep walking’ was added to the existing product information.

- Report all suspected reactions to medicines that display a black triangle (▼). The symbol is a prompt to alert health professionals to report all suspected ADRs for products displaying it regardless of the reaction’s severity or seriousness.

- It’s useful to supply supplementary information such as relevant medical history and tests to help us with assessment.

- Remember - it’s quicker to report directly to the MHRA via the Yellow Card Scheme: www.mhra.gov.uk/yellowcard

Corn plasters and skin ulceration (patients/physicians)

A podiatric physician (foot doctor) contacted the MHRA regarding concerns over medicated corn removal plasters that contained salicylic acid. Two patients who had healthy skin and had used these plasters went on to develop ulcers at the application site. This triggered a review of

reactions that had been reported in association with this type of plaster in contact with healthy skin.

MHRA experts assessed the seven reports associated with salicylic acid-containing plasters, on the Yellow Card database. These Yellow Cards reported mainly suspected skin reactions. The pharmaceutical company was requested to review the safety of the product and provide a response to MHRA.

This resulted in the following new wording for the product information: “local irritation or dermatitis may occur if applied to normal healthy skin surrounding the corn. This may be controlled by temporarily discontinuing use and by careful applying only to the corn when the treatment is returned.”

- Only a suspicion is required that a medicine may be causing a reaction to report – no matter how minor: www.mhra.gov.uk/yellowcard

Tiotropium bromide (Braltus) and choking

A woman in her sixties was taking Braltus for chronic obstructive pulmonary disease (COPD). COPD is the name for a group of lung conditions that cause breathing difficulties. It is used to describe progressive lung diseases such as emphysema, chronic bronchitis, and non-reversible asthma. Braltus is prescribed in the form of an inhalation powder within a hard capsule and is administered using a Zonda inhaler. The Zonda inhaler has a dust cap that opens up to a mouthpiece below where there is a centre chamber. To take the medicine, the Braltus capsule is placed into the centre chamber and a button is pressed to pierce the capsule and the patient inhales the medicine through the mouthpiece. By piercing the capsule within the centre chamber, the powdered medicine is released and so can be inhaled when the patient breathes in via the mouthpiece.

A pharmacy assistant from the medicines management team in her area submitted a Yellow Card on behalf of a patient who inadvertently/accidentally inserted the Braltus capsule into the mouthpiece of the Zonda inhaler, instead of putting the capsule into the centre chamber for piercing. When the patient tried to inhale to take the medicine, the capsule was sucked into her mouth and went to the back of her throat. The patient quickly coughed the capsule back out, however this could have choked her. The pharmacy assistant highlighted in the Yellow Card report that the shape design of the Zonda inhaler allowed the capsule to be incorrectly placed into the mouthpiece and this presents a choking risk for patients.

This was the only Yellow Card report the MHRA received for this specific issue. However, the MHRA also received an enquiry from a specialist pharmacist regarding this problem, which was based on evaluation of the device before prescribing opposed to an actual safety incident. The specialist pharmacist was a Medication Safety Officer (MSO). MSOs were established after a joint patient safety alert issued by NHS England and MHRA in 2014 to increase reporting and to increase local and national learning from patient safety incidents, including medication errors. Since 2014, a National Medication Safety Network of MSOs, operating in partnership with NHS Improvement (NHSI), MHRA and Specialist Pharmacy Service, has been in place with monthly virtual meetings intended as a forum for discussing potential and recognised safety issues as well as for identifying trends and actions to improve the safe use

of medicines. In England, most MSOs are hospital pharmacists, and they continue to report as well as encourage reporting within their trusts. In addition to improving the quality of reporting, the MSOs serve as the essential link between the identification and implementation of local and national medication safety initiatives and the daily activities to improve patient safety with the use of medicines.

Upon receipt of the above evidence, the scientific assessor investigating the issue conducted a detailed investigation of all the available safety data. This often includes routine liaison with the Defective Medicines Report Centre (DMRC) at the MHRA to see if any similar safety data has been received via this route. DMRC stated that a pharmacist had reported that a practice nurse found that when she was demonstrating the Braltus Zonda inhaler to an elderly COPD patient using a dummy device for training, that the patient placed the capsule for inhalation in the mouthpiece rather than the centre chamber. The nurse rightly raised the concern that patients may become confused, as they are able to place capsules into the mouthpiece and if they then use the inhaler the whole capsule will be inhaled, leading to choking, as well as not taking the needed medicine.

Safety signals that contain a medicine and a device are considered by the MHRA's Drug Device Combination (DDC) expert group who were also concerned about this issue, given the potential severity of inhaling a capsule. As a result, the MHRA met with the pharmaceutical company that manufactures the product, resulting in changes to the instructions for use (IFU), including new pictograms showing the correct way to insert a capsule into the device as well as a new warning to avoid the risk of choking which included the advice for patients and users of the product that capsules should never be placed directly into the mouthpiece of the inhaler. Similar pictograms and the same warning were also included on the inside of the carton lid. A Drug Safety Update (DSU) article was subsequently issued by the MHRA to further inform healthcare professionals of the safety issue. Drug Safety Update is the MHRA's monthly bulletin to inform healthcare professionals of the latest issues in medicines safety.

- Yellow Cards can be reported for medicines which work in combination with a device; for example, an inhalation capsule and inhaler.

- The MHRA can sometimes take regulatory action on as little as one report – if you suspect a safety issue then speak to your healthcare professional and report it to the Yellow Card Scheme.

- The MHRA works closely with groups such as the National Medication Safety Network of Medication Safety Officers to encourage the safe use of medicines, encourage Yellow Card reporting, and for both local and national learning from incidents and medication errors.

- Anyone can subscribe to Drug Safety Update email alerts via the MHRA's website: https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency/email-signup.

Cetalkonium chloride and choline salicylate (Bonjela) and swollen tongue

An elderly woman was using Bonjela for tongue pain. Bonjela contains cetalkonium chloride and choline salicylate. After using Bonjela, the woman suffered from a swollen tongue, which when shown to the pharmacy assistant was so severe that it was considered a possible choking hazard and the ambulance was called for further assistance who provided the patient with oxygen therapy.

The pharmacy assistant checked and no information regarding the potential for a swollen tongue, or other hypersensitivity reactions were documented within the Patient Information Leaflet (PIL) for Bonjela. The pharmacy assistant submitted a Yellow Card online to inform the MHRA of what happened to the patient and her suspicions that it might be associated with the Bonjela therapy.

During routine assessment of the Yellow Card report and considering the lack of information regarding this type of side effect within the PIL, a detailed investigation was initiated. Further review revealed four additional cases, received between 2001 and 2017, reporting swollen tongue with Bonjela. Two of these reports were received from a hospital pharmacist, one from a hospital healthcare professional and the remaining report from a GP. All four reports concerned adult patients. Two of the four patients were admitted to hospital as a result of the suspected reaction. A broader search revealed 29 Yellow Cards with hypersensitivity type reactions, in the absence of a swollen tongue, reported in association with Bonjela.

The side effect was discussed in further detail by a multidisciplinary team at the MHRA. The safety review concluded that as Bonjela is available over the counter and contains a derivative of salicylic acid, which is known to be associated with hypersensitivity type reactions, therefore it was deemed there was biological plausibility for the side effects experienced by the patients to be caused by Bonjela. This resulted in regulatory action and the product information for Bonjela was updated by the pharmaceutical company with the addition of new warnings of hypersensitivity in the undesirable effects section. The patient information leaflet supplied with the medicine in the box was also updated by the pharmaceutical company to include a warning regarding unexplained wheezing or coughing, asthma, shortness of breath, difficulty breathing, itching, face, tongue or throat swelling, which can all be signs of serious allergic reactions and what to do if you experience any of these signs.

- If you are concerned about a side effect, ask your doctor or pharmacist for advice.
- Any healthcare professional can report suspected side effects to the Yellow Card Scheme, not just doctors and pharmacists.
- Yellow Card reporting is valuable even for over the counter (OTC) medicines which have been marketed for long periods of time; previously unrecognised side effects are still being identified.
- Always read the product information for a product.

Perindopril and Raynaud's phenomenon

A Yellow Card report was sent in by a man in his sixties who was prescribed perindopril for high blood pressure, his perindopril treatment was later switched to ramipril. He was unsure of the exact date that his medicines were switched and uncertain of when he began to experience his symptoms where his fingers would become white, cold and numb during cold weather. The man suspected these might be side effects experienced from taking both perindopril and ramipril. He reported that over a few years, these suspected side effects became more frequent affecting multiple fingers and both hands, and more severe, with his skin becoming dark red/purple and giving a painful tingling sensation. He reported that this was happening on an almost daily basis. His condition was diagnosed as Raynaud's phenomenon. Raynaud's phenomenon is a condition where arteries spasm and can cause episodes of reduced blood flow, often to outer parts of the body, resulting in pain or changes in colour in the area in which it occurs. After stopping the medicine, the symptoms had almost completely gone away within a few days.

Routine review of this Yellow Card report involved an additional search for other similar reports of suspected Raynaud's type reactions that were reported to be suspected in association with perindopril use. Five additional Yellow Card reports were reviewed, dated between 1991 and 2013. Four of these were submitted by GPs and one from a healthcare professional who had not specified their qualification on the Yellow Card report. Within the Yellow Card reports, patients ages ranged between 40 and 90 years old with one male and four females. None of the Yellow Card reports suspected any other medications than perindopril. Most cases reported the side effects appearing within a few days to a week of starting perindopril, whilst one reported the reaction occurring within an hour. One of the Yellow Cards even reported that the side effects occurred when the dose was increased from 2mg to 4mg. In all instances, the suspected side effects experienced by the patients were reported to be recovering or had recovered on stopping perindopril.

The MHRA noted that Raynaud's phenomenon is listed as a known side effect for many of the drugs within the same class as perindopril, known as an angiotensin-converting enzyme (ACE) inhibitor. ACE inhibitors work by relaxing and widening the blood vessels which in turn lowers blood pressure and makes it easier for the heart to pump blood around the body. This can improve the symptoms of heart failure. However, Raynaud's phenomenon was not listed in the product information for any perindopril products. Due to the way in which perindopril is licensed, the MHRA raised this safety concern to the European Medicines Agency (EMA) who asked the pharmaceutical company to submit a review of all cases of perindopril and Raynaud's phenomenon. The review was then evaluated by the EMA who requested that the product information for perindopril was updated to include Raynaud's phenomenon as a potential side effect, as per MHRA's considered recommendations.

- If you are concerned about any suspected side effects, speak to your doctor or pharmacist for advice.

- Yellow Card reports from patients are proven to provide a valuable contribution to effective medicines regulation and pharmacovigilance.

- Four simple things are needed to complete a Yellow Card report:

    1) Suspected medicine

2) Suspected side effect

One piece of information about both the:

3) Patient and
4) Reporter

- Providing extra information helps the assessment of Yellow Cards by MHRA experts and other international medicines regulators.

Varenicline and transient loss of consciousness

The MHRA also collects reports of suspected adverse drug reactions from other countries associated with medicines used within the United Kingdom. One such report from Denmark concerned a woman taking varenicline (Champix) for smoking - cessation therapy. A fortnight after starting Champix, she experienced alcohol poisoning as she had been drinking alcohol whilst on Champix. The patient suddenly had a blackout and couldn't remember how long it had lasted. She then began to shake and was feeling unwell. Although other factors within this report were considered to have potentially contributed to the loss of consciousness, it was still considered to be a potential serious concern for UK patients, especially if this reaction occurred whilst driving.

A routine review of the safety information identified 37 UK reports, received between 2007 and 2017, involving the combination of suspected varenicline and the suspected effect of loss of consciousness. Of these, twenty-four cases were received directly through the Yellow Card Scheme by patients (four) and healthcare professionals (twenty), and thirteen more reports were received from the pharmaceutical industry who are legally obliged to report any suspected adverse drug reactions reported to them to the MHRA. During the analysis of the safety information within these reports, thirty-one cases specified that only varenicline was suspected to have been associated with the loss of consciousness; no other suspected medications were considered to have been involved. Eight reports contained other factors relevant to a loss of consciousness, including intake of alcohol, seizures, hypoglycaemia (low blood sugar) or a fall. However, several the Yellow Card reports provided strong evidence that therapy with varenicline in the absence of any other potentially contributory factors could result in a loss of consciousness.

Some concern was felt as section 4.7 of the product information, entitled 'Effects on ability to drive and use machines', mentioned dizziness and somnolence (sleepiness) but not loss of consciousness. A patient may read this and think they would have time to pull over safely once the reaction started. However, there were a number Yellow Card reports where the patient lost consciousness without warning or fell asleep suddenly, posing a real danger to those patients who drive regularly or use machinery.

Due to the way in which varenicline is licenced, this safety issue was raised to the European Medicines Agency (EMA) by the MHRA for further review. Following the safety review, the risk of a transient loss of consciousness was added to the product information within the undesirable effects section as well as the relating sections on the ability to drive and use machinery.

- Report concerns of suspected side effects directly to the MHRA rather than to the pharmaceutical company.

- The MHRA routinely reviews all available safety information not just within the UK but including information across the globe from other medicines regulatory databases.

- Your Yellow Card report adds information which contributes to the safety profile of a medicine and reports help the MHRA monitor the safety of medicines over time to enable robust evidence-based decision making. Don't delay, report today.

Charcoal and drug interaction: impaired absorption of other medicines resulting in ineffectiveness

Activated charcoal is an intestinal absorbent which at lower dosages is used for the treatment of indigestion. A hospital pharmacist submitted a Yellow Card report after seeing a woman in her seventies who was taking several medications; amoxicillin and clarithromycin for a chest infection as well as candesartan, bisoprolol and furosemide which are commonly used to treat heart failure. The patient was admitted to hospital with worsening heart failure symptoms and worsening atrial fibrillation whilst at the same time her chest infection had also not resolved. The pharmacist was concerned that the woman was possibly taking charcoal at the same time of day as her other medication and that this was leading to impaired absorption of the medicines resulting in their not working as well as they should. Although there was a warning stating *'if on medication or if you have an unusual reaction to contact your doctor or pharmacist'* on the container of the charcoal product, the pharmacist had concerns that its visibility and location on the packaging might not be prominent enough for patients to take notice of.

A thorough literature review was conducted. No other similar reports were on the Yellow Card database. This safety issue was discussed by colleagues within the specialist Self Medication Unit at the MHRA. It was concluded that charcoal did have the potential to reduce the absorption of other medicines, and that patients should seek advice from a pharmacist or doctor if any other medication is being taken when starting therapy with charcoal. Regulatory action was taken by the MHRA and the pharmaceutical company updated the product information to include a potential interaction between charcoal and other medicinal products, an update of the charcoal product's packaging to incorporate a better design and increased prominence of the warning regarding its use with other medicines, including advice to read the product information leaflet before use.

- Taking multiple medicines is often necessary but can increase the chance of side effects and interactions. It's important to read the leaflet and report suspect interactions and side effects.

- Yellow Card reporting can lead to changes in product packaging and design.

- The MHRA monitors the safety of all medicines to protect patients from harm and encourages Yellow Card reports no matter how medicines are obtained e.g. over the

counter (OTC), bought themselves, or via a prescription – this includes herbal medicines too.

Labetalol and nipple pain

A pregnant woman reported a Yellow Card report about crippling nipple pain, a burning sensation, localised tingling and blanching of the nipple whilst she was taking labetalol for high blood pressure during her pregnancy. Each time, the pain would last for around 20 minutes. She mentioned that she experienced the same side effects during a previous pregnancy when she also took labetalol. The patient expressed her concerns that she had described her symptoms to several healthcare professionals, none of which were aware of any association between the symptoms she was experiencing and labetalol.

A routine safety review by MHRA experts, identified 6 other similar UK reports of labetalol in association with nipple pain, received between 2009 and 2017, all in pregnant women. Two of which were reported directly to the Yellow Card Scheme by the patient themselves, the other four Yellow Card reports were submitted by healthcare professionals. The cases ranged across ages, all at differing stages in their pregnancies. Most cases reported that the nipple pain was recovering after stopping the medicine used to treat their high blood pressure.
This safety signal was discussed with a multi-disciplinary MHRA team. It was noted that breast tissue undergoes significant changes during pregnancy under the influence of hormones such as estrogen, progesterone and prolactin including changes in the blood vessels and growth of lobules for milk production. However, whilst these changes could result in the nipple pain observed in the case reports, the time to onset provided in many of the cases closely coincided with the changes in nipple colour mentioned by many patients - all of which are a sign of Raynaud's phenomenon. Raynaud's phenomenon is a condition where arteries spasm and can cause episodes of reduced blood flow, often to outer parts of the body, resulting in pain or changes in colour of the area in which it occurs. Several of the Yellow Card reports detailed the effects occurring specifically after the labetalol dose and some reported recovery after labetalol withdrawal. Raynaud's phenomenon is listed in the product information as a known side effect of labetalol therapy. It was deemed plausible that manifestation of this in the nipples could occur. Since this was not specifically listed in the product information, it was thought it may be helpful to include, particularly for patients who aren't familiar with what the condition may entail.

Regulatory action was taken directly by the MHRA to ask the relevant pharmaceutical companies to update their Patient Information Leaflet (PIL) for labetalol to include nipple pain as a possible symptom of Raynaud's Phenomenon.

- Some women will need to take medicines to protect their health and that of the baby. Women who are pregnant or breastfeeding, or who are planning a pregnancy, should talk to their healthcare professional about medicines they are taking.

- When a medicine is licensed, there is often limited information on effects from use in pregnancy. Reporting any suspected side effects from the use of medicines in pregnancy is vitally important to ensure that health professionals and women have the best available information on safe use.

- Pregnant women, breastfeeding mothers, parents and carers can report any suspicions of side effects that are suspected to be associated with a medicine on a Yellow Card.

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

- The MHRA encourages Yellow Card reports from healthcare professionals who work with pregnant women such as obstetricians and midwives and their assistants, who can provide key information such as results from prenatal scans and background information surrounding a pregnancy.

Rivaroxaban (Xarelto ▼) and drug administration error: Patients taking rivaroxaban on an empty stomach and developing thromboembolic events

A hospital pharmacist reported that a female patient had been taking rivaroxaban treatment 15mg twice daily for a diagnosed deep vein thrombosis (the formation of a blood clot in a deep vein). The woman took her medicine at home on an empty stomach – the Patient Information Leaflet (PIL) states that *you must take Xarelto together with a meal* for both the 15mg and 20mg tablet forms. The woman ended up being admitted to hospital with shortness of breath. A computed tomography pulmonary angiogram (*CTPA*) was performed which diagnosed a pulmonary embolism (a blood clot in the lung). This proved that the rivaroxaban was not effective in providing anticoagulation that it was prescribed for.

Through a routine safety review, two other Yellow Cards were identified in which patients were also taking on an empty stomach and went on to experience a thrombotic event. The first concerned a male patient, who took rivaroxaban 20mg daily for 3 days, alongside olanzapine, for deep vein thrombosis (DVT). He experienced a pulmonary haemorrhage and decreased haemoglobin. His healthcare professional noted that the patient took the medicine on an empty stomach in the morning when he doesn't eat breakfast. The second additional case involved an elderly male patient taking rivaroxaban 15mg daily to prevent a stroke. Three days after starting therapy, he experienced a fatal ischemic stroke. The doctor considered this could have been due to the fact that the patient didn't know rivaroxaban should be taken with food.

This safety issue was further discussed within the MHRA, and it was noted that the advice provided in the patient information leaflet on taking rivaroxaban with food is in line with the approved guidelines. However, due to the seriousness of the Yellow Card reports and the severity of harm which could occur if rivaroxaban is not taken with food, the pharmaceutical company was requested to update the product information for the 15mg and 20mg medicinal products and to re-order the information under the section called *How to take Xarelto* ▼ to make it even clearer these doses should be taken with food.

To increase awareness of this issue amongst healthcare professionals, a Drug Safety Update (DSU) article was published to remind them that Xarelto ▼ should always be taken with food.

- Report all suspected side effects to new medicines under additional monitoring (▼) directly to the MHRA using the online Yellow Card reporting form or the app.

- Reporting known effects of medicines via Yellow Cards can be important in clarifying information presented to patients and highlighting important information about the safe use of medicines and potential risks to protect public health and raising awareness on clinical particulars, including administration of medicines.

- Patients should always read the patient information leaflet supplied with their medicines. It lists all recognised side effects and interactions; as well as directions on when to administer the medicine.

Propranolol and abnormal weight gain

A concerned female patient emailed the MHRA querying whether we had received reports of other patients who had been taking propranolol that experienced abnormal weight gain. This woman started to experience gradual weight gain a month taking propranolol for a month. She described it as generally starting off as a pound per week (0.45kg/week) for about a month to two months, but then it began to increase to about two pounds per week (0.9kg/week). The patient decided to make radical diet changes as a result of the weight gain and is now weaning herself off propranolol.

The patient spotted that weight gain was not documented as a known side effect of propranolol therapy within the Patient Information Leaflet that came with her medicine. Upon reviewing the query further investigation identified nine other cases of propranolol in association with abnormal weight gain, dated between 2014 and 2018. These Yellow Cards were all reported directly by the patients themselves and involved both men and women between the ages of 30 and 70 years. The reports demonstrated good temporal association with the medication – in other words, many patients experienced the weight gain soon after starting and then lost the weight upon stopping the propranolol.

Propranolol belongs to a group of medicines called beta blockers. When reviewed, it was noted that abnormal weight gain is a known side effect of other drugs within this class. Furthermore, it was noted that beta blockers can interfere with carbohydrate and insulin regulation and this could potentially lead to weight gain in patients who take the drug. Following discussion by a multidisciplinary team at the MHRA, it was concluded that the pharmaceutical companies that manufacture propranolol should be requested to update their product information to include the possible side effect of abnormal weight gain, to ensure that patients are aware of all possible adverse events when taking the medicine.

- If you are worried about your health, including side effects, always speak to a healthcare professional.

- Always read the patient information leaflet – It lists the known side effects or problems and advises you on what to do. If a side effect is not listed, speak to a healthcare professional and report a Yellow Card.

- Don’t forget to always report suspected adverse reactions to the Yellow Card Scheme – you don’t need anyone’s permission to report and only a suspicion is needed to submit a Yellow Card.

- Yellow Card reports from patients are proven to provide a valuable contribution to effective medicines regulation and pharmacovigilance.

- Your report matters. Reporting suspected side effects directly to the Yellow Card Scheme helps the safer use of medicines and improved patient safety.