

Contribution of Yellow Cards to identifying safety issues

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.

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

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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
September 2016	Posaconazole (Noxafil)	Tablets and oral suspension are not directly interchangeable	Strengthened product information warnings to clarify the oral solution cannot be substituted for the oral tablet, or vice versa, at the same dose. The outer packaging was changed to better distinguish the difference in the two formulations. Drug Safety Update (DSU) article published.

June 2016	Etonogestral (Nexplanon)	Device found in vasculature and lung	Updated advice via DSU for healthcare professionals on how to correctly insert the implant, including an amended diagram in the SmPC that illustrates the correct angle on the arm for insertion and how to view the needle to avoid deep insertion.
June 2016	Dexamethasone and Ritonovir	Drug interaction: increase the risk of systemic adrenal effects	Strengthened product information warnings detailing the drug interaction of systemic adrenal effects.
April 2016	Natalizumab (Tysabri ▼)	Progressive Multifocal leukoencephalopathy (PML)	Strengthened product information warnings about PML including risk factors and risk minimisation measures. A direct healthcare professional communication (DHPC) was sent out to healthcare professionals to highlight the importance of monitoring through testing patients every 6 months to reduce risk of PML.
December 2015	Cobicistat and fluticasone	Drug interaction: increase the risk of adrenal suppression	Strengthened product information warnings about the drug interaction increasing the risk of adrenal suppression after this was raised through the EU system. DSU article published.
May 2015	Warfarin	Calciphalex	Strengthened product information warnings and information about calciphalex even with normal renal function, with advice to consult a doctor a painful skin rash develops. DSU article published.
February 2015	Medroxyprogesterone acetate (Sayana)	Injection site atrophy	Strengthened product information warnings of injection site atrophy
November 2014	Gaviscon Infant	Constipation	Strengthened product information warnings of constipation
October 2014	Proton Pump Inhibitors (PPIs)	Subacute cutaneous lupus erythematosus (SCLE), a non-	Strengthened product information warnings of SCLE, including information for

		scarring dermatosis that can develop in sun-exposed areas	healthcare professionals and patients or carers about lesions especially in sun-exposed areas of the skin and accompanied by arthralgia. DSU article published.
October 2014	Interferon beta (Rebif, Avonex, Betaferon, Extavia)	Thrombotic microangiopathy (TMA) and suspicion of increased risk with new formulation of Rebif	Collaborative assessment with NIBSC. Need for better risk minimisation identified. Class warnings implemented for all products. Warnings to be vigilant for early signs or symptoms issued and added to the product information including diagnostic tests descriptions, treatment options and advice on the action to take. Further requirements were made for the pharmaceutical company to do further study on the possible increased risk of TMA with new formulation Rebif.
September 2014	Pregabalin	Abuse, misuse and dependence	Strengthened product information warnings regarding abuse, misuse and dependence
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 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 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

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

Corticosteroids 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, nifedipine, nimodipine and verapamil. Grapefruit does not affect diltiazem.
- immunosuppressants such as ciclosporin, 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 reactions 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