Medicines & Healthcare products Regulatory Agency

Drug Safety Update

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

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Contents

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

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

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First, we inform healthcare professionals that the Isotretinoin Expert Working Group of the Commission on Human Medicines has made recommendations to strengthen the safety of isotretinoin treatment for severe acne. While processes to support the implementation of these recommendations across the healthcare system are being developed, prescribers of isotretinoin are reminded of the need to fully inform all patients of the potential benefits and risks associated with isotretinoin treatment and monitor patients closely for any side effects throughout treatment. See page 2 for more information.

In our second article we advise of new risk minimisation measures for Janus kinase (JAK) inhibitors, used to treat chronic inflammatory disorders, which are consistent with the measures introduced for the JAK inhibitor tofacitinib in 2020 and 2021. See page 7 for more information.

Next, we remind healthcare professionals prescribing nitrofurantoin, an antibiotic used for urinary tract infections, to be alert to the risks of pulmonary and hepatic adverse drug reactions. We ask prescribers to advise patients to be vigilant for important signs and symptoms that warrant further investigation.

On page 15, we include recent letters, recalls, and notifications sent to healthcare professionals about medicines and medical devices. If you have been forwarded this issue of Drug Safety Update, subscribe directly via our website.

Isotretinoin (Roaccutane▼): new safety measures to be introduced in the coming months, including additional oversight on initiation of treatment for patients under 18 years

The Isotretinoin Expert Working Group of the Commission on Human Medicines has made recommendations to strengthen the safety of isotretinoin treatment. Recommendations include new warnings, the need for consistent monitoring requirements for psychiatric side effects, the introduction of new monitoring requirements for sexual side effects, and additional oversight of the initiation of treatment for patients younger than 18 years.

While processes to support the implementation of these recommendations across the healthcare system are being developed, prescribers of isotretinoin are reminded of the need to fully inform all patients of the potential benefits and risks associated with isotretinoin treatment and monitor patients closely for any side effects throughout treatment.

No new action from healthcare professionals is needed for now – further communications will be issued once these recommendations are being implemented.

Information on the safety review:

- the Commission on Human Medicines (CHM) and its Isotretinoin Expert Working Group has recommended new measures to strengthen the safety of isotretinoin treatment – see report and summary report of the recommendations
- recommendations include the addition of new warnings for the risk of sexual dysfunction, including the possibility of persistence after treatment discontinuation, and advice for healthcare professionals to ask patients about symptoms or signs of sexual dysfunction prior to starting treatment with isotretinoin and to monitor patients for the development of new sexual disorders during treatment
- recommendations also include the development of consistent monitoring requirements for potential psychiatric and sexual side effects in all patients throughout treatment
- the initiation of treatment in patients younger than 18 years will require 2 prescribers to agree a patient's acne is severe and that there is no other effective treatment before initiation of isotretinoin therapy
- the CHM has formed an Implementation Advisory Group, which is composed of experts and representatives of healthcare organisations, to advise on the implementation of these recommendations
- no new action is needed from healthcare professionals for now, but we ask prescribers to fully discuss the risks with patients considering isotretinoin

Advice for healthcare professionals:

- isotretinoin is indicated for severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic anti-bacterials and topical therapy
- continue to follow strict precautions on prescribing isotretinoin, including the conditions of the isotretinoin Pregnancy Prevention Programme
- fully inform patients about the potential risks in addition to the expected benefits before prescribing isotretinoin
- assess an individual's mental health before initiation of isotretinoin and monitor regularly for developing or worsening psychiatric disorders
- tell patients to seek advice if they feel their mental health or sexual function is affected or is worsening – patients with a serious side effect should be told to stop their treatment and seek urgent medical advice
- report suspected adverse drug reactions associated with isotretinoin on a Yellow Card

Advice for healthcare professionals to provide to patients and caregivers:

- isotretinoin is effective for severe types of acne, especially if there is a risk of permanent scarring, but like every medicine it is associated with a risk of side effects
- isotretinoin should only be used when other treatments for acne have not worked
- not every patient has side effects, but you should know about the risks and what to do if they occur — read the leaflet that comes with your medicine to learn about the risks associated with isotretinoin
- take time to think about the information from your doctor about the benefits and risks of isotretinoin, and decide if isotretinoin is the right treatment for you
- report side effects associated with isotretinoin directly to the MHRA via the Yellow Card scheme

Isotretinoin indication and potential risks

Isotretinoin is a treatment for severe acne. It should only be prescribed to treat severe forms of acne that have not responded to other treatments, such as antibiotics and topical treatments (creams or gels). Isotretinoin capsules are also known by the brand names Roaccutane and Reticutan in the UK.

Isotretinoin has a number of important risks, including causing significant harm to an unborn baby if used during pregnancy. Blood testing is required for all patients on isotretinoin to monitor for abnormalities associated with hepatobiliary disorders and lipid metabolism.

Suspected psychiatric disorders and cases of sexual dysfunction have also been reported by patients on isotretinoin and these issues should be managed promptly (see section below).

Isotretinoin Expert Working Group Review

In September 2019, the Commission on Human Medicines (CHM) formed the Isotretinoin Expert Working Group (IEWG) to review the safety of isotretinoin, in particular concerns about suspected psychiatric and sexual side effects and whether, in some cases, these continue after use of isotretinoin has been stopped (see Drug Safety Update, August 2020).

The IEWG considered the available information on psychiatric and sexual side effects suspected to be associated with isotretinoin. This included suspected side effects reported to the MHRA via the Yellow Card scheme, research into the risks and the biological mechanisms that may explain these events, from published studies about patients taking isotretinoin, and information on how isotretinoin safety is managed in other countries. A public call for information resulted in 659 responses with views from patients, families, and other stakeholders and more than 7 hours of direct presentations, which were considered carefully by the IEWG in making its recommendations.

The recommendations of the expert safety review are available in the Report of the Commission on Human Medicines Isotretinoin Expert Working Group and the plain-language summary of the recommendations.

Recommendations from the review

The IEWG considered all the available evidence, including information from patients and their families and concluded that gaps in the available evidence meant that it was not possible to say that isotretinoin definitely caused many of the short-term or longer-term psychiatric and sexual side effects. However, the individual experiences of patients and families continue to cause concern and the Group emphasised the need for patients to be informed about the risks before starting isotretinoin treatment, for there to be additional oversight of prescribing in young patients under 18, and for patients to be consistently monitored for side effects. Following the review and endorsement by the CHM, the MHRA will be introducing a number of measures to strengthen the safety of isotretinoin.

Isotretinoin should not be used for the treatment of prepubertal acne and is not recommended in children younger than 12 years of age. For patients younger than 18 years of age, there will also be a requirement for two prescribers to jointly agree that the acne is severe enough to justify treatment with isotretinoin and that other standard treatments have been sufficiently tried and were ineffective before isotretinoin is started. There will be further communication when this requirement is implemented.

The product information for isotretinoin medicines is being updated with these new requirements and to add new information and warnings regarding psychiatric and sexual disorders. This will include a warning that there have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of isotretinoin.

The product information will state that patients, and where applicable their families, must be counselled about the risk of psychiatric side effects and sexual dysfunction prior to prescription of isotretinoin. Patients should have an assessment of their mental health and sexual function prior to treatment and should be monitored during treatment for developing psychiatric or sexual disorders.

The CHM has established an Implementation Advisory Expert Working Group to

- advise on pathways and strategies to implement the recommendations
- help develop communication and educational materials for patients to support and record informed prescribing decisions
- advise on how to monitor compliance and effectiveness of these new measures
- advise and make recommendations on future research and a registry

The Implementation Advisory Expert Working Group is composed of experts and representatives of the healthcare organisations who will be involved in the implementation of these recommendations.

Advice for healthcare professionals during implementation

While processes to support the implementation of these recommendations across the healthcare system are being developed, healthcare professionals should continue to follow the existing strict precautions on prescribing isotretinoin. This includes the need to counsel patients on the potential risks of isotretinoin.

Warnings for psychiatric disorders

Depression, anxiety, and psychotic symptoms have been reported in patients treated with isotretinoin, and there have been cases where patients on isotretinoin died by suicide. More information on the suspected adverse drug reactions reported are included in the CHM report.

Prescribers should discuss the risks of psychiatric disorders with patients and their caregivers fully before starting isotretinoin treatment. This should include a discussion on the importance of seeking medical attention if their mental health is affected. It is recommended that patients taking isotretinoin ask their family and friends to watch out for potential symptoms of psychiatric disorders. Updated materials for patients are being developed for people taking isotretinoin.

All patients taking isotretinoin should have an assessment of their mental health before starting treatment and be monitored regularly for signs of psychiatric symptoms by their

prescriber and referred for appropriate treatment if necessary. Discontinuation of isotretinoin may not be effective in alleviating symptoms and therefore further psychiatric or psychological evaluation may be necessary.

Warnings for sexual dysfunction

Use of isotretinoin may be associated with sexual dysfunction. Reported suspected side effects include erectile dysfunction and decreased libido, vulvovaginal dryness, orgasm difficulties, and genital hypoaesthesia. More information on the suspected adverse drug reactions reported are included in the CHM report. There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of isotretinoin.

Patients should be asked about the presence of symptoms or signs of sexual dysfunction prior to starting treatment with isotretinoin, and be monitored for the development of new sexual disorders during treatment. The age and maturity of the patient should be considered in choosing the most appropriate counselling approach, including giving the option to discuss without parents or carers present where appropriate. Appropriate guidelines should be considered when providing advice about sexual health to young people.

Report any reactions on a Yellow Card

Isotretinoin is a black triangle medicine and all suspected adverse reactions, including any sexual and psychiatric adverse reactions, should be reported via the Yellow Card scheme. Reports can be made of suspected reactions experienced at any time, including historic adverse experiences with medicines.

Please include in the report as much detail as possible, particularly if a side effect continued or started after treatment was stopped. Information about medical history, any concomitant medication, onset timing, treatment dates, and product brand name should also be included.

Report to the Yellow Card scheme electronically using:

- the Yellow Card scheme website
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

Article citation: Drug Safety Update volume 16, issue 9: April 2023: 1.

Janus kinase (JAK) inhibitors: new measures to reduce risks of major cardiovascular events, malignancy, venous thromboembolism, serious infections and increased mortality

We inform healthcare professionals of new risk minimisation measures for JAK inhibitors used to treat chronic inflammatory disorders, consistent with the measures introduced for tofacitinib (Xeljanz) in 2020 and 2021. This advice affects abrocitinib (Cibinqo▼), baricitinib (Olumiant), upadacitinib (Rinvoq▼), and filgotinib (Jyseleca▼) when used for chronic inflammatory disorders.

Advice for healthcare professionals:

- an increased incidence of malignancy, major adverse cardiovascular events (MACE), serious infections, venous thromboembolism (VTE) and mortality, when compared to those treated with tumour necrosis factor (TNF)-alpha inhibitors, has been observed in trials of patients with rheumatoid arthritis with certain risk factors when treated with some JAK inhibitors, particularly tofacitinib – see advice for tofacitinib from 2020 and 2021
- following a review, these risks are considered class effects across JAK inhibitors used for chronic inflammatory disorders and therefore it is advised to avoid prescribing these medicines unless there are no suitable alternatives in patients with the following risk factors:
    - age 65 years or older
    - current or past long-time smoking
    - other risk factors for cardiovascular disease or malignancy
- use caution if prescribing in patients with risk factors for VTE other than those listed above (see below for more details)
- where applicable, use lower doses in patients with risk factors (see individual Summary of Product Characteristics of each medicine for further detail – abrocitinib (Cibinqo), baricitinib (Olumiant), upadacitinib (Rinvoq), and filgotinib (Jyseleca))
- the incidence of non-melanoma skin cancer in the study was also higher with tofacitinib than with a TNF inhibitor – therefore carry out periodic skin examinations in all patients on JAK inhibitor medicines to check for signs of skin malignancy
- inform patients of these risks and key signs and symptoms that could warrant urgent medical attention (see below)
- report suspected adverse drug reactions associated with JAK inhibitors on a Yellow Card

Advice for healthcare professionals to provide to patients and caregivers:

- JAK inhibitors are effective medicines for treating chronic inflammatory disorders such as severe arthritis, psoriatic arthritis, inflammatory bowel diseases, and atopic eczema (atopic dermatitis)
- however, these medicines can increase a patient's risk of developing major cardiovascular problems (such as heart attack or stroke), cancer, blood clots in the lungs and in the deep veins of the body, serious infections, and death when compared with other treatments for these conditions called TNF-alpha inhibitors
- the risks are greater if you have risk factors, such as being age 65 years or older, have an already increased risk of major cardiovascular problems or cancer, or if you smoke or have smoked in the past for a long time
- if you have a risk factor, your doctor will consider alternative treatment options and only offer you treatment with a JAK inhibitor if nothing else is suitable for you
- your doctor may recommend a lower dose of the JAK inhibitor medicine, to minimise possible risks
- contact your doctor or seek urgent medical advice if, during treatment, you experience chest pain or tightness (which may spread to arms, jaw, neck and back), shortness of breath, cold sweats, light headedness, sudden dizziness, weakness in arms and legs or slurred speech – these are signs of a medical emergency
- examine your skin periodically and let your doctor or nurse know if you notice any new growths on your skin or changes to moles (including itching, shape and discharge, which may not be as obvious on darker skin tones); these could require investigation for possible skin cancer
- always read the leaflet that accompanies your medicines and talk to your doctor, nurse, or pharmacist if you are concerned about side effects

Background

Janus kinase (JAK) inhibitors are a class of medicines that include Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib), and Xeljanz (tofacitinib). They are used in the treatment of chronic inflammatory disorders such as rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, ulcerative colitis, Crohn's disease, atopic dermatitis, and alopecia areata. See specific product information for further detail – abrocitinib (Cibinqo), baricitinib (Olumiant), upadacitinib (Rinvoq), and filgotinib (Jyseleca).

This advice is not relevant for use of JAK inhibitors (ruxolitinib (Jakavi▼) and fedratinib (Inrebic▼) to treat myeloproliferative disorders, nor Olumiant used outside of the licence in the short-term treatment of COVID-19.

Risks previously identified for Xeljanz (tofacitinib)

In 2020, the results of a clinical safety trial in patients with rheumatoid arthritis aged 50 years or older with at least one cardiovascular risk factor (Study A3921133; the phase 3B/4 randomised safety endpoint trial)[1] found that tofacitinib was associated with an increased risk of major adverse cardiovascular events (MACE, defined as death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke), malignancies, VTE, and serious and fatal infections, compared with TNF-alpha inhibitors (etanercept or adalimumab).

Prescribers of tofacitinib were informed of the trial findings and the recommended risk minimisation measures in a letter and Drug Safety Update in 2020 and a further letter and Drug Safety Update in 2021. The tofacitinib product information and educational materials were updated at this time.

Further information on the incidence rates and hazard ratios for these events in the tofacitinib groups compared with the TNF-alpha inhibitor group can be found in the letters for healthcare professionals relating to venous thromboembolism and serious and fatal infections (2020) and major adverse cardiovascular events and malignancies (2021).

Given the findings, we advised that tofacitinib should not be used in patients older than 65 years of age, people who are current or past smokers, or individuals with other cardiovascular (such as diabetes or coronary artery disease) or malignancy risk factors unless there are no suitable treatment alternatives.

Review of the risks across the class of JAK inhibitors

Following the findings for tofacitinib, a broader review was conducted by the European Medicines Agency in 2022, looking at all JAK inhibitors indicated for inflammatory diseases.

As well as the results of study A3921133 for tofacitinib, the review considered the preliminary findings of a multi-database observational cohort study of baricitinib (Olumiant) treatment (study B023), which also suggested an increased risk of major cardiovascular events (incidence rate ratio (IRR) 1.92; 95% CI 1.27 to 2.91) and VTE (IRR 1.34; 95% CI 0.84 to 2.14) in patients with rheumatoid arthritis treated with Olumiant compared with those treated with TNF-alpha inhibitors.

The latest review looked at the available mechanistic and safety data for each of the 5 JAK inhibitors approved as treatments for inflammatory conditions. The review concluded that the effects could be considered a class effect, while acknowledging that

the extent to which the findings of study A3921133 applied to all JAK inhibitors was dependent on the similarities of each treated population in terms of the presence of risk factors.

The MHRA reviewed the recommendations together with information relevant to the use of these medicines in the UK and sought independent advice from the Pharmacovigilance Expert Advisory Group of the UK's Commission on Human Medicines. Following this review, changes are being made to the product information for all JAK inhibitor medicines authorised for inflammatory diseases to note the updated risk characterisation and expanded risk minimisation measures. A letter has also been sent to UK healthcare professionals to advise of these changes.

Information on updated risk factors

Based on the data assessed, some updates to the existing warnings for tofacitinib were recommended and these will be implemented for all JAK inhibitors included in the review.

The advice across the class of medicines on the need for caution in use in patients with risk factors for VTE was updated to include VTE risk factors, which are distinct from the cardiovascular and malignancy risk factors mentioned elsewhere. VTE risk factors other than cardiovascular or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, and inherited coagulation disorders.

In the previous update to the tofacitinib product information, it was advised that tofacitinib should only be used in current or past smokers if no suitable treatment alternatives are available, as current or past smoking were identified as predictive factors for development of MACE and malignancies. Further analysis of this risk factor in participants of study A3921133 found that more than 90% of tofacitinib-treated patients who were current or past smokers had a smoking duration of more than 10 years and a median of 35.0 and 39.0 smoking years, respectively. The warnings on MACE and malignancy for all JAK inhibitors have therefore been updated from past smoking to specify long-time past smoking as a risk factor, in addition to current smoking.

Post-hoc analyses of study A3921133 showed that a history of atherosclerotic cardiovascular disease (a composite of coronary artery disease, cerebrovascular disease, or peripheral artery disease) is a risk factor for MACE. Therefore, the warning on MACE for all JAK inhibitors is being updated to include history of atherosclerotic cardiovascular disease as a risk factor.

Increased all-cause mortality is being added as a risk for patients 65 years of age and older.

Where possible, lower doses are recommended for patients with risk factors for these serious side effects (see individual product information for specific advice).

Report suspected reactions on a Yellow Card

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the Yellow Card website
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

When reporting suspected adverse drug reactions, please provide as much information as possible, including information about medical history, any concomitant medication, onset timing, and treatment dates. When reporting for a biological medicine or vaccine, please ensure that you provide the brand name (or product licence number and manufacturer), and the specific batch number.

Article citation: Drug Safety Update volume 16, issue 9: April 2023: 2.

Reference

1. Ytterberg SR and others. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. New England Journal of Medicine 2022. Issue 386; pages 316 to 326.

Nitrofurantoin: reminder of the risks of pulmonary and hepatic adverse drug reactions

Healthcare professionals prescribing nitrofurantoin should be alert to the risks of pulmonary and hepatic adverse drug reactions and advise patients to be vigilant for the signs and symptoms in need of further investigation.

Advice for healthcare professionals:

- advise patients and caregivers to be vigilant for new or worsening respiratory symptoms while taking nitrofurantoin and promptly investigate any symptoms that may indicate a pulmonary adverse reaction
- pulmonary reactions may occur with short- or long-term use of nitrofurantoin, and increased vigilance for acute pulmonary reactions is required in the first week of treatment
- patients receiving long-term therapy, for example for recurrent urinary tract infections, should be closely monitored for new or worsening respiratory symptoms, especially if elderly
- immediately discontinue nitrofurantoin if new or worsening symptoms of pulmonary damage occur
- be vigilant for symptoms and signs of liver dysfunction in patients taking nitrofurantoin for any duration, but particularly with long-term use, and monitor patients periodically for signs of hepatitis and for changes in biochemical tests that would indicate hepatitis or liver injury
- use caution when prescribing nitrofurantoin in patients with pulmonary disease or hepatic dysfunction, which may mask the signs and symptoms of adverse reactions
- advise patients to read carefully the advice in the Patient Information Leaflet about symptoms of possible pulmonary and hepatic reactions and to seek medical advice if they experience these symptoms
- report suspected adverse drug reactions (ADRs) to the Yellow Card scheme

Advice for healthcare professionals to give to patients and caregivers:

- nitrofurantoin is an effective antibiotic used to prevent and treat infections of the bladder, kidney, and other parts of the urinary tract, but it has been linked to side effects affecting the lungs and liver
- if you are taking nitrofurantoin, seek medical advice if you experience trouble breathing, shortness of breath, a lingering cough, coughing up blood or mucus, or pain or discomfort when breathing. These may be symptoms of a side effect affecting the lungs
- talk to your doctor or another healthcare professional promptly if you develop yellowing of the skin or eyes, upper right abdominal pain, dark urine and pale or grey-coloured stools, itching or joint pain and swelling. These may be symptoms of a side effect affecting the liver

Pulmonary damage and nitrofurantoin

Nitrofurantoin is a broad-spectrum antibacterial agent, which has been available since the 1950s. It is indicated in adults, children and infants over 3 months old for:

- treatment and prophylaxis of acute or recurrent uncomplicated urinary tract infections (UTIs)
- treatment and prophylaxis of acute or recurrent uncomplicated pyelitis

The NICE guidelines on antimicrobial prescribing for UTIs recommend nitrofurantoin as one of the first choices, particularly if there is a high risk of trimethoprim resistance (for example NICE guideline 109). Treatment courses for infections are indicated to last between 3 and 7 days. However, some patients may be given a daily dose as prophylaxis for recurrent UTIs.

Reports of acute pulmonary damage

The MHRA has received a Coroner's report following the death of a patient who experienced acute pulmonary damage and respiratory failure after being treated with nitrofurantoin for a UTI for a 10-day course. The Coroner raised concerns about the known risk of acute pulmonary damage following nitrofurantoin treatment and the need to highlight this to healthcare professionals and patients.

The potential for acute pulmonary damage with nitrofurantoin is well-documented in the product information for nitrofurantoin. The Summary of Product Characteristics (SmPC) states that acute, subacute and chronic pulmonary adverse reactions have been observed in patients treated with nitrofurantoin. Symptoms of acute pulmonary reactions usually include fever, chills, cough, chest pain, dyspnoea, pulmonary infiltration with consolidation or pleural effusion on chest X-ray, and eosinophilia. For subacute pulmonary reactions, fever and eosinophilia occur less often than in the acute form.

Information from published studies on the frequency or severity of pulmonary ADRs in association with acute use of nitrofurantoin is limited. A precise estimate of frequency of these ADRs, and the frequency of fatal outcomes cannot be made, but evidence from observational studies[1,2] suggests that the pulmonary ADRs in association with acute use of nitrofurantoin are infrequent.

If symptoms of pulmonary damage occur, nitrofurantoin should be discontinued immediately. The Patient Information Leaflet (PIL) advises patients that lung adverse reactions may occur and that patients should consult a doctor immediately if they notice symptoms of a lung reaction. Close monitoring of pulmonary conditions is advised for patients receiving long-term therapy (especially elderly people). Patients and carers should be reminded about the symptoms of pulmonary damage and the need to seek prompt medical advice if they experience these symptoms.

Following advice from the Pharmacovigilance Expert Advisory Group of the Commission on Human Medicines, Marketing Authorisation Holders for these medicines have been requested to strengthen the wording in the UK SmPC and PIL. These updates will include the advice that healthcare professionals should be vigilant for respiratory symptoms in patients taking nitrofurantoin, for any duration, and promptly investigate these symptoms, as they may indicate a pulmonary reaction.

Reminder of the risk of hepatic reactions

Following discussions with NHS England, we would like to remind healthcare professionals of the risk of hepatic adverse drug reactions and clarify our advice on the frequency of monitoring.

Nitrofurantoin can rarely cause hepatic reactions, including cholestatic jaundice, chronic active hepatitis, autoimmune hepatitis, and hepatic necrosis. Events with a fatal outcome have been reported. Nitrofurantoin should be discontinued immediately if hepatitis occurs.

The onset of hepatitis may be gradual and may not have obvious symptoms at first. It is important to monitor patients periodically for changes in biochemical tests that could indicate hepatic dysfunction and for clinical signs or symptoms of liver abnormality, especially in patients taking long-term nitrofurantoin.

When scheduling periodic monitoring, take into account relevant local guidance, as well as any pre-existing conditions that might mask the symptoms of a hepatic reaction and the patient's ability to recognise symptoms and seek advice in the event of a hepatic reaction. This periodic monitoring may be an opportunity to remind patients about the possible symptoms of hepatic reactions and to remind them to seek medical advice if they experience these symptoms.

Report any suspected adverse drug reactions

Please continue to report suspected adverse drug reactions to nitrofurantoin via the Yellow Card scheme. Your report will help us safeguard public health.
Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the Yellow Card website
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

When reporting, please provide as much information as possible, including information about batch numbers, medical history, any concomitant medication, onset timing, treatment dates, and product brand name.

Article citation: Drug Safety Update volume 16, issue 9: April 2023: 3.

References

1. Claussen K and others. How Common Are Pulmonary and Hepatic Adverse Effects in Older Adults Prescribed Nitrofurantoin? Journal of the American Geriatric Society 2017; volume 65, pages 1316 to 1320.
2. Jick SS and others. Hospitalizations for pulmonary reactions following nitrofurantoin use. Chest 1989; volume 96, pages 512 to 515.

Letters and medicine recalls sent to healthcare professionals in March 2023

Letters

In March 2023, the following letters were sent or provided to relevant healthcare professionals:

- Hydroxycarbamide 100 mg/ml oral solution (Xromi): Changes to the oral syringes copackaged with Xromi
- Ozempic▼solution for injection in pre-filled pen (semaglutide): supply shortage in the UK
- Cibingo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) and Xeljanz (tofacitinib) – Updated recommendations to minimise the risks of malignancy, major adverse cardiovascular events, serious infections, venous thromboembolism and mortality with use of Janus kinase inhibitors (JAKi)
- Sabril 500mg granules for oral solution (vigabatrin): Interim Supply of Italian Stock to Mitigate Supply Disruption

Medicine Recalls and Notifications

In March 2023, recalls and notifications for medicines were issued on:

Class 2 Medicines Recall: Teva UK Limited, Levothyroxine 12.5mcg Tablets, EL (23)A/06. Issued 2 March 2023. Teva UK Limited is recalling one batch of Levothyroxine 12.5mcg Tablets in response to a lower than required assay result discovered during routine stability testing. Healthcare professionals should stop supplying the affected batch immediately, quarantine all remaining stock and return it to the supplier.

Class 4 Medicines Defect Information: Thornton & Ross Ltd, Methadone 1mg/mL Oral Solution BP - Sugar Free, Methadone Mixture 1mg/ml, EL(23)A/07. Issued 7 March 2023. Specific batches of Methadone 1mg/mL Oral Solution BP Sugar Free and Methadone Mixture 1mg/ml, have been packaged with the incorrect Product Information Leaflet (PIL). Links to the correct PILs are provided in the notice.

Class 4 Medicines Defect Information: Drugsrus Limited, Clexane 10,000 IU (100mg) / 1ml Syringes, EL(23)A/08. Issued 9 March 2023. The Patient Information Leaflet (PIL) packaged in specific batches of Clexane 10,000IU (100mg)/1 ml Syringes contains a typographical error. The strength of the product listed in the leaflet header states “100,000 IU (100mg) / 1ml” instead of “10,000 IU (100mg)/1ml”. The remainder of the packaging states the correct strength of 10,000 IU (100mg)/1ml. There is no risk to product quality. Healthcare professionals are advised to tell patients about the error and reassure them that they have the right dose of medicine.

Class 2 Medicines Recall: Various Marketing Authorisation Holders, pholcodine-containing products, EL (23)A/09. Issued 14 March 2023. Following the conclusion of a review of post-marketing safety data by the MHRA, all pholcodine-containing medicines are being recalled and withdrawn from the UK as a precaution. Healthcare professionals should stop supplying the products listed in this recall immediately. Quarantine all remaining stock and return it to your supplier. Healthcare professionals should recommend appropriate treatment alternatives. Where appropriate, healthcare professionals should also check whether patients who are scheduled to undergo general anaesthesia with neuromuscular blocking agents (NMBAs) have used pholcodine, particularly in the previous 12 months, and remain vigilant for the risk of anaphylaxis in these patients. Patients should be advised to tell their anaesthetist if they think they have previously taken pholcodine.

Class 4 Medicines Defect Information: Macarthys Laboratories t/a Martindale Pharma, Venlafaxine XL 150mg, 225mg, 300mg prolonged-release tablets, EL(23)A/10. Issued 16 March 2023. In addition to the batches included in the previous Class 4 Medicines Notification (reference EL(22)A/47), Martindale Pharma has made the MHRA aware that the GTIN in the 2D barcode and the printed variable data represents the branded version of the product (Venlalic® XL prolonged-release tablets). It should instead reflect the generic name: Venlafaxine XL prolonged-release tablets. The code under the pre-printed barcode is correct. There is no risk to product quality as a result of this issue. Healthcare professionals are advised to exercise caution when dispensing the products.

Class 3 Medicines Recall: Rosemont Pharmaceuticals Limited, Sildenafil 10mg/ml Oral Suspension, EL(23)A/11. Issued 21 March 2023. The Press In Bottle Adaptor (PIBA) supplied with the pack (carton) of a specific batch is too wide to fit the neck of the medicine bottle. Healthcare professionals should stop supplying the affected batch immediately, quarantine all remaining stock and return it to the supplier. There is no risk to product quality.

Class 2 Medicines Recall: Ferring Pharmaceuticals Limited, GONAPEPTYL Depot 3.75mg, Powder and solvent for suspension for injection, EL(23)A/12. Issued 23 March 2023. Ferring Pharmaceuticals Limited is recalling certain batches of GONAPEPTYL Depot 3.75mg due to a defect identified in the seal of the needle wrapping for the CE-marked 30-millimeter (30mm) needle for subcutaneous injection that is supplied with each product pack. Slight damage was detected in some sterile needle blisters, which renders the sealing to be incomplete. There is no quality issue with the drug product. Healthcare professionals should stop supplying the affected batches immediately, quarantine all remaining stock and return it to the supplier.

Class 4 Medicines Defect Information: Ethigen Limited, Briviact 75mg & 100mg film-coated tablets, EL(23)A/13. Issued 30 March 2023. The Patient Information Leaflet (PIL) in Briviact 75mg and Briviact 100mg film coated tablets contains incorrect or missing information due to a formatting error. There is no risk to product quality as a result of this issue. Healthcare professionals are advised to exercise caution when dispensing the affected batches of the product. Where possible, please provide an updated copy of the PIL to the patient and remind the patient to read the leaflet in its entirety before using the medicine.

Medical Device Safety Information

We recently published a Device Safety Information page on the following topic:

Belzer UW Cold Storage Solution and Belzer MPS UW Machine Perfusion Solution manufactured by Carnamedica (UKRP: Bridge to Life): Contamination of fluid (update to DSI/2023/002), DSI/2023/005

This Device Safety Information replaces advice in DSI/2023/002, which should no longer be followed. The manufacturer (Carnamedica) has identified a number of issues with their third-party suppliers of Belzer UW Cold Storage Solution and Belzer MPS UW Machine Perfusion Solution. Concerns have been raised about the aseptic filling process, leak testing of the bags and the conditions under which filled bags are stored and transported.

The latest advice includes an updated list of LOTs associated with defect reports, additional problems identified with the solution, and new actions for healthcare professionals. The MHRA continues to work with Carnamedica and Bridge to Life (UK Responsible Person) and may provide further updates as new information is identified.

Belzer UW Cold Storage Solution (CSS) is intended for flushing and cold storage of kidney, liver and pancreas organs at the time of their removal from the organ donor in preparation for storage, transportation and eventual transplantation into a donor recipient.

Belzer UW Machine Perfusion Solution (MPS) is intended for the in-vitro flushing and continuous hypothermic machine perfusion preservation of explanted kidneys.

Bridge to Life issued an updated Field Safety Notice dated 1 March 2023, broadening the scope of the corrective action.

The list of problems identified to date is:

- microbiological contamination
- particulate matter within the solution
- leakage of fluid
- growth of black mould on the exterior of the connectors

An investigation is ongoing into the root cause of the problems identified and, therefore, unlisted LOT numbers are not guaranteed to be unaffected by these issues. LOT numbers involved in confirmed reports are provided in the Devices Safety Information page to support stakeholders in providing increased vigilance to patients who have received organs where affected lots were used.

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