NHS
Kent and Medway

Nitrofurantoin safety
Monitoring guidance for prescribers

Key Points from the Alert[1]

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.

MHRA Advice for healthcare professionals:[1]

- 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, website here

Recommended monitoring for patients who are prescribed nitrofurantoin

Before starting long term Nitrofurantoin consider:[2][3][4]

- Baseline LFTs
- Baseline U&Es & eGFR - Contraindicated if eGFR is less than 30mL/minute/1.73m^2.
- If eGFR less than 45 mL/min/1.73m^2, normally avoid unless used with caution as a short course only (3 to 7 days). Indications include uncomplicated lower urinary tract infection caused by suspected or proven multi-drug resistant bacteria where benefit outweighs risk.
- Where possible chest examination & oxygen saturations to be performed prior to initiating long term nitrofurantoin by the clinician initiating this treatment, or the clinician requesting this be prescribed by another prescriber, for example within an outpatient setting.
- G6PD deficiency (contraindicated if deficiency) and porphyria (contraindicated)
- On initiation patients should be provided with the nitrofurantoin safety leaflet and informed of the need to report any side effects/symptoms straight away.

Longer term review[4]

- Patients should be reviewed within 6 months of starting nitrofurantoin. To reduce the risk of antimicrobial resistance, at each review:
    - women should be reminded about self-care

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- consideration should be given to either stopping, continuing or changing antibiotic prophylaxis
- The decision on when to stop, continue or change antibiotic prophylaxis depends on the circumstances of an individual person.
- Liver function tests (LFTs) should be checked at baseline and every 3-6 months
- Renal function should be checked at baseline and every 3-6 months
- Close monitoring of pulmonary conditions is advised, especially in elderly people[1]

Treatment should be stopped immediately:[4]

1) if pulmonary toxicity is suspected or detected
2) at the first sign of hepatotoxicity
3) at the first sign of neurological involvement.
4) Haematological toxicity[2]

Review treatment if renal function drops below 45 ml/minute.

Background information - Pulmonary toxicity[4]

- The potential for acute pulmonary damage with nitrofurantoin is well-documented in the SPC which states that acute, subacute and chronic pulmonary adverse reactions have been observed in patients treated with nitrofurantoin.[2]
- If symptoms of pulmonary damage occur, nitrofurantoin should be discontinued immediately.
- Acute pulmonary reactions usually occur within the first week of treatment and are reversible on cessation of therapy.[4] Symptoms of acute pulmonary reactions usually include fever, chills, cough, chest pain, dyspnoea, pulmonary infiltrates/ consolidation/ pneumonitis on chest x-ray (usually bilateral) or pleural effusion on chest X-ray, fine late inspiratory crackles on auscultation, restricted vital capacity on spirometry (indicates severe disease), peripheral eosinophilia on blood tests.
- In sub-acute pulmonary reactions, fever and eosinophilia occur less often than in the acute form.
- Chronic pulmonary reactions (including pulmonary fibrosis and interstitial lung disease) can develop insidiously with minor symptoms, more commonly in elderly patients. The severity of chronic pulmonary reactions and their degree of resolution appear to be related to the duration of therapy after the first clinical signs appear. It is important to recognise symptoms as early as possible as lung injury may be permanent due to fibrosis, even after cessation of therapy.

Patients receiving long-term nitrofurantoin should be made aware of the symptoms of pulmonary toxicity and the importance of reporting these to their GP if they occur.

Background information - Hepatic toxicity[4]

- Hepatic reactions including cholestatic jaundice and chronic active hepatitis occur rarely, but fatalities have been reported.
- Cholestatic jaundice is generally associated with short-term therapy (usually up to 2 weeks). Chronic active hepatitis, occasionally leading to hepatic necrosis is generally associated with long-term therapy (usually after 6 months). The onset may be insidious.
- Treatment should be stopped at the first sign of hepatotoxicity.

Patients receiving long-term nitrofurantoin should have liver function checked at baseline[2] and every 3-6 months.

Background information - Renal impairment[4]

- Nitrofurantoin is contraindicated in patients suffering from renal impairment with an eGFR < 45 ml/minute, although it may be used with caution as short-course therapy only for the treatment of uncomplicated lower urinary tract infection in individual cases with an eGFR between 30-44 ml/min to treat resistant pathogens, when the benefits are expected to outweigh the risks.

Patients receiving long-term nitrofurantoin should have renal function checked at baseline[2] and every 3-6 months.

Neurological toxicity[4]

- Peripheral neuropathy (including optical neuritis) with symptoms of sensory as well as motor involvement, which may become severe or irreversible have been reported
- Treatment should be stopped at the first sign of neurological involvement

Recurrent urinary tract infections[6]

Kent and Medway local antibiotic prescribing guidance and NICE guidance recommend:

- First advise about behavioural and personal hygiene measures, and self-care (with D-mannose or cranberry products) to reduce the risk of UTI.
- For postmenopausal women, if no improvement, consider vaginal oestrogen (review within 12 months).
- For non-pregnant women, if no improvement, consider single-dose antibiotic prophylaxis for exposure to a trigger (review within 6 months).
- For non-pregnant women (if no improvement or no identifiable trigger) or with specialist advice for pregnant women, men, children or young people, consider a trial of daily antibiotic prophylaxis (review within 6 months).
- Trimethoprim or nitrofurantoin are the first choice antibiotics for prophylaxis for people 16 years and over, with amoxicillin and cefalexin as second choice options.
- Nitrofurantoin 50 – 100mg daily at night is an option for long-term low dose prophylaxis of recurrent UTIs in patients with eGFR ≥45 ml/minute.
- A review within 6-months is recommended as this reflects the duration of most trials of prophylactic antibiotics and information on long-term follow-up is lacking.

References:

1. MHRA Drug Safety Update. Nitrofurantoin: reminder of the risks of pulmonary and hepatic adverse drug reactions. Available at: Nitrofurantoin: reminder of the risks of pulmonary and hepatic adverse drug reactions - GOV.UK (www.gov.uk)

2. SPS Medicines Monitoring. Nitrofurantoin Monitoring. Published 5 July 2021.

3. Summary of Product Characteristics. Nitrofurantoin 100mg capsules Nitrofurantoin 100mg Capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

4. Previous East Kent Prescribing Group Guidance for Nitrofurantoin Monitoring

5. Recurrent UTIs in Women. Bristol, North Somerset and South Gloucestershire CCG guidance. Available at https://remedy.bnssg.icb.nhs.uk/media/6268/recurrent-utis-in-women-version-21.pdf

6. NICE Visual Summary Guidance 'UTI (recurrent): antimicrobial prescribing. Available at :NG112 UTI (recurrent): antimicrobial prescribing visual summary (nice.org.uk)

Acknowledgements

1. **Original East Kent Prescribing Group document adapted from guidance written by Telford and Wrekin CCG**

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