Surrey Heartlands
HEALTH AND CARE PARTNERSHIP

Prescribing and Monitoring Guidance for Nitrofurantoin in Primary Care

Nitrofurantoin- Key Prescribing Points:

- **Avoid concurrent use with over the counter (OTC) products for cystitis:** OTC products containing potassium or sodium citrate salts relieve symptoms by making the acidic urine (resulting from the bacterial infection) more alkaline. However, urine alkalisation reduces the effect of nitrofurantoin[1]
- **Caution when prescribing nitrofurantoin in patients with pulmonary disease or hepatic dysfunction** as the signs and symptoms of adverse reactions may be masked in these patient groups.[2]
- **Advise patients to read carefully the advice in the Patient Information Leaflet** : which will inform about symptoms of possible pulmonary and hepatic reactions and to seek medical advice if they experience these symptoms.[2]
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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 tummy pain on the right hand side, 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.

- **Immediately discontinue nitrofurantoin if new or worsening symptoms of pulmonary damage occur:** Pulmonary reactions may occur with short or long-term use of nitrofurantoin. Increased vigilance for acute pulmonary reactions is required in the first week of treatment.[2]
- **Be vigilant for symptoms and signs of liver dysfunction:** in patients taking nitrofurantoin for any duration, but particularly with long-term use.
- **Long-term/ prophylaxis: monitor Renal Function Tests, Liver Function Tests, pulmonary symptoms and signs of hepatitis every 6 months.** Consider similar monitoring for repeated treatment courses. More frequent monitoring (every 3 months) should be considered for the elderly and/or where there are concerns about a patients clinical condition, concomitant drugs, or comorbidities.[3] Pulmonary function can be monitored by symptom assessment and spirometry (if available).
- **Do <u>not</u> use for upper urinary tract infection (UUTI):** Nitrofurantoin only achieves antibiotic concentration in the urine. Low circulating blood levels and poor tissue penetration makes it unsuitable for the treatment of upper UTIs.
- **Poor Renal function- avoid if GFR < 45mls/min:** Nitrofurantoin is preferentially excreted into the lower urinary tract (approx 30-40%). If eGFR < 30mls/min - therapeutic concentrations unlikely to be obtained and treatment failure likely. eGFR should

preferably be ≥ 45mls/min (if eGFR between 30-44mls/min use only if no other options and for short courses of 3-7 days.[4]

- **Pregnancy and lactation- avoid in pregnant women at term and avoid in breast feeding:** Animal studies with nitrofurantoin have shown no teratogenic effects. However, it is contraindicated in infants < 3 months of age and in pregnant women during labour and delivery, due to possible risk of haemolysis of the infants' immature red cells. Breast feeding an infant known or suspected to have an erythrocyte enzyme deficiency (including G6PD deficiency) must be temporarily avoided since nitrofurantoin is detected in trace amounts in breast milk.[1]
- **Consult NICE guidelines** for information on alternative treatment options in urinary tract infections.[5]

This guidance is intended to support:

- Prescribing recommendations for urinary tract infection as part of the NICE Summary of Antimicrobial Guidance[5]
- Monitoring guidance as part of the Specialist Pharmacy Services (SPS) Drug Monitoring Tool[6] : Recommendations for tests prior to starting treatment with nitrofurantoin (long-term) are included; however for ongoing monitoring (long term/prophylaxis) the recommendations are that the frequency needs to be determined locally.

The Medicines and Healthcare products Regulatory Agency drug safety update on the risks of pulmonary and hepatic adverse drug reactions to nitrofurantoin.[2]

Pulmonary Symptoms: Nitrofurantoin is one of the commonest causes (although relatively rare) of drug induced pulmonary disease/toxicity, which can potentially be serious and even fatal. Pulmonary toxicity can be either acute or chronic. Acute pulmonary reactions usually occur within the first week of treatment and are reversible when treatment is stopped. Acute symptoms include: fever, chills, cough, chest pain, breathlessness, and chest x-ray abnormalities.[7] Interstitial Pulmonary fibrosis (IPF) is a rare condition and can be associated with the use of nitrofurantoin. If pulmonary toxicity is suspected / detected, nitrofurantoin should be stopped immediately. Chronic pulmonary reactions (including IPF) can develop insidiously and can include mild fever, chills, persistent cough, breathlessness, tiredness and clubbing of the fingers. If pulmonary symptoms are not detected early and are allowed to progress, this can become irreversible and, in some cases, fatal. Monitoring of pulmonary symptoms for patients on long-term prophylaxis is therefore very important, and should be checked at least every 6 months (see above). Patients should also be advised to report any symptoms suggestive of pulmonary toxicity, such as cough, chest pain and shortness of breath. Regular review of the continued requirement for prophylaxis is also important particularly in the elderly. MHRA advice is to discontinue if there is a deterioration in lung function for patients on long-term therapy.[2]

Hepatotoxicity: Hepatic reactions, including hepatitis, autoimmune hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic necrosis, occur rarely. Fatalities have been reported. The onset of chronic active hepatitis may be insidious, and patients should be monitored periodically for changes in biochemical tests that would indicate liver injury. If hepatitis occurs, the drug should be withdrawn immediately and appropriate measures should be taken. For long term treatment, monitor the patient closely for appearance of hepatic or pulmonary symptoms and other evidence of toxicity.[1]

References:

1) Electronic Medicines Compendium (eMC): https://www.medicines.org.uk/emc/
2) Medicines and Healthcare products Regulatory Agency. Drug safety update Nitrofurantoin: reminder of the risks of pulmonary and hepatic adverse drug reactions. April 2023
3) Local agreement on frequency for ongoing monitoring by the Surrey Heartlands Antimicrobial Stewardship (AMS) Collaborative Working Group June 2020
4) British National Formulary (BNF) : https://bnf.nice.org.uk/drug/nitrofurantoin.html [Accessed May 2023]
5) NICE/PHE Common Infections Guidance: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/antimicrobial%20guidance/summary-antimicrobial-prescribing-guidance.pdf
6) Specialist Pharmacy Services (SPS) : Medicines Monitoring Tool. Accessed May 2023:
7) British Lung Foundation (BLF) : Pulmonary Fibrosis: https://www.blf.org.uk/support-for-you/pulmonary-fibrosis/symptoms [Accessed May 2023]