May 19, 2023

Direct healthcare-professional communication (DHPC) Nitrofurantoin: reminder of the risks of pulmonary and hepatic adverse drug reactions

Dear Healthcare Professional,

Acino Pharma AG in agreement with Saudi Food and Drug Authority (SFDA) would like to remind you of the following regarding safe use of nitrofurantoin medicinal products:

Summary

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 carefully read 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 to the SFDA National Pharmacovigilance & Drug Safety Centre (NPC)

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.

Further information on the safety concern and the recommendations

Nitrofurantoin is a broad-spectrum antibacterial agent, which has been available since the 1950s. It is indicated for:

- Acute infections of the efferent urinary tract, particularly if there is resistance to other antimicrobial agents.
- Chronic infections of the efferent urinary tract.
- Infection prophylaxis in diagnostic examinations or following surgery on the urinary tract system.

Risk of pulmonary adverse drug reactions

Acute, subacute and chronic pulmonary reactions have been observed in patients treated with nitrofurantoin.

Acute pulmonary reactions usually occur within the first week of treatment and are reversible with cessation of therapy. Acute pulmonary reactions are commonly manifested by fever, chills, cough, chest pain, dyspnoea, pulmonary infiltration with consolidation or pleural effusion on chest x-ray, and eosinophilia. In subacute pulmonary reactions, fever and eosinophilia occur less often than in the acute form [2].

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

The subacute pulmonary reactions, which can normally occur approximately 1 month after nitrofurantoin therapy, is characterised by dyspnoea, orthopnoea, fever, persistent cough and interstitial pneumonia and/or pulmonary fibrosis. However, fever and eosinophilia are observed more rarely. Improvement is more gradual upon discontinuation of the product.

Symptoms of the chronic form, which can occur after approximately 6 months of nitrofurantoin therapy, are those of the subacute form. Associated symptoms and damage are only partially reversible. Chronic pulmonary reactions (including pulmonary fibrosis and diffuse interstitial pneumonitis) may occur commonly in elderly patients. Close monitoring of the pulmonary condition of patients receiving long-term therapy is warranted, especially in the elderly [1].

If symptoms of pulmonary damage occur, nitrofurantoin should be discontinued immediately.

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 [1].

Risk of hepatic adverse drug reactions

Hepatic reactions including hepatitis, autoimmune hepatitis, cholestatic jaundice chronic active hepatitis and hepatic necrosis, occur rarely. Events with a fatal outcome 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.

Cholestatic jaundice is generally associated with short-term therapy (usually up to two weeks). Chronic active hepatitis, occasionally leading to hepatic necrosis is generally associated with long-term therapy (usually after six months) [1].

Treatment should be stopped at the first sign of hepatotoxicity. If hepatitis occurs, the drug should be withdrawn immediately, and appropriate measures should be taken.

The onset of hepatitis may be gradual. 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. Pre-existing conditions should be taken into account that might mask the symptoms of a hepatic reaction and the patient's ability to recognise symptoms.

Patients should be warned about the possible symptoms of hepatic reactions and reminded to seek medical advice if they experience these symptoms [2].

Further information

For more details, please refer to Uvamin™ 100 mg retard capsules Summary of Product Characteristic.

Call for reporting

Healthcare professionals are encouraged to report adverse events in patients taking nitrofurantoin to **SFDA NPC**

Fax: +966-11-205-7662
Call NPC at 8002490000 (free phone)
SFDA call centre: 19999
E-mail: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa

Acino contact points

For reporting of adverse events:
- 24/7 phone: +966-55-3561871
- E-mail: pvksa@acino.swiss

For medical information requests:
E-mail: MIRMETA@acino.swiss

DocuSigned by:
Eva Kopecna
F21FCAD33D37430...

Dr. med. Eva Kopecna, MSc., Ph.D.
Global Head of Regulatory Affairs,
Medical and Pharmacovigilance
Acino International

DocuSigned by:
Manshi Areej
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Pharm.D. Areej M. Manshi
Qualified Person Responsible for
Pharmacovigilance (QPPV) KSA
Acino Scientific Office Riyadh KSA

References:

1. Uvamin™ 100 mg retard capsules KSA approved SmPC. Date of revision of the text: Nov 2019. Uvamin™ 100 mg retard capsules Registration Certificate of Pharmaceutical Product # 10-222-99 date 31/ 07/ 2019
2. Nitrofurantoin: reminder of the risks of pulmonary and hepatic adverse drug reactions, published by Medicines and Healthcare products Regulatory Agency on 26 April 2023, available at https://www.gov.uk/drug-safety-update/nitrofurantoin-reminder-of-the-risks-of-pulmonary-and-hepatic-adverse-drug-reactions accessed 10.05.2023