

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NIFURAN 50 mg, capsules, hard

Nitrofurantoin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg of nitrofurantoin as active substance.

3. PHARMACEUTICAL FORM

Capsules, hard.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For the treatment of and prophylaxis against acute or recurrent, uncomplicated lower urinary tract infections or pyelitis either spontaneous or following surgical procedures.

Nitrofurantoin is specifically indicated for the treatment of infections when due to susceptible strains of *Escherichia coli*, enterococci, staphylococci, *Citrobacter*, *Klebsiella* and *Enterobacter*.

4.2. Posology and method of administration

Posology

Adults

Acute Uncomplicated Urinary Tract Infections (UTIs):

50 mg four times daily for seven days.

Severe chronic recurrence (UTIs):

100 mg four times daily for seven days.

Long term suppression:

50-100 mg once a day.

Prophylaxis:

50 mg four times daily for the duration of procedure and for three days thereafter.

Paediatric population

Children and Infants over three months of age

Acute Urinary Tract Infections: 3mg/kg day in four divided doses for seven days.

Suppressive - 1mg/kg, once a day.

Elderly

Provided there is no significant renal impairment, in which nitrofurantoin is contraindicated, the dosage should be that for any normal adult. See precaution and risks to elderly patients associated with long-term therapy (see section 4.8).

Renal impairment

Nitrofurantoin is contraindicated in patients with renal dysfunction and in patients with an eGFR of less than 45 ml/minute (see sections 4.3 & 4.4).

Method of administration

For oral use.

4.3. Contraindications

Hypersensitivity to the active substance, other nitrofurans or to any of the excipients listed in section 6.1.

- Patients suffering from renal dysfunction with an eGFR of less than 45 ml/minute.

Nitrofurantoin 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.

- G6PD deficiency (see also Section 4.6)
- Acute porphyria.
- In infants under three months of age as well as pregnant patients at term (during labour and delivery) because of the theoretical possibility of haemolytic anaemia in the foetus or in the newborn infant due to immature erythrocyte enzyme systems.

4.4. Special warnings and precaution for use

Nitrofurantoin is not effective for the treatment of parenchymal infections of unilaterally nonfunctioning kidney. A surgical cause for infection should be excluded in recurrent or severe cases.

Since pre-existing conditions may mask adverse reactions, nitrofurantoin should be used with caution in patients with pulmonary disease, hepatic dysfunction, neurological disorders, and allergic diathesis.

Peripheral neuropathy and susceptibility to peripheral neuropathy which may become severe or irreversible has occurred and may be life threatening. Therefore, treatment should be stopped at the first signs of neural involvement (paraesthesia).

Nitrofurantoin should be used in caution with patients with anaemia, diabetes mellitus, electrolyte imbalance, debilitating conditions and vitamin B (particularly folate) deficiency.

Acute, subacute and chronic pulmonary reactions have been observed in patients treated with nitrofurantoin. If these reactions occur, nitrofurantoin should be discontinued immediately.

Chronic pulmonary reactions (including pulmonary fibrosis and diffuse interstitial pneumonitis) can develop insidiously, and may occur commonly in elderly patients. Close monitoring of the pulmonary condition of patients receiving long-term therapy is warranted (especially in the elderly).

Patient should be monitored closely for signs of hepatitis (particularly in long term use). Urine may be coloured yellow or brown after taking nitrofurantoin. Patients on nitrofurantoin are susceptible to false positive urinary glucose (if tested for reducing substances).

nitrofurantoin should be discontinued at any sign of haemolysis in those with suspected glucose-6-phosphate dehydrogenase deficiency.

Gastrointestinal reactions may be minimised by taking the drug with food or milk, or by adjustment of dosage.

Discontinue treatment with nitrofurantoin if otherwise unexplained pulmonary, hepatic, haematological or neurological syndromes occur.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicinal products and other forms of interaction

- Increased absorption with food or agents delaying gastric emptying.
- Decreased absorption with magnesium trisilicate.
- Decreased renal excretion of nitrofurantoin by probenecid and sulfinpyrazone.
- Decreased anti-bacterial activity by carbonic anhydrase inhibitors and urine alkalinisation.
- Anti-bacterial antagonism by quinolone anti-infectives.
- Interference with some tests for glucose in urine.
- Typhoid Vaccine (oral): Antibacterials inactivate oral typhoid vaccine.

4.6. Fertility, pregnancy and lactation

Pregnancy

Animal studies with nitrofurantoin have shown no teratogenic effects. Nitrofurantoin has been in extensive clinical use since 1952, and its suitability in human pregnancy has been well documented. However, as with all other drugs, the maternal side effects may adversely affect course of pregnancy. The drug should be used at the lowest dose as appropriate for a specific indication, only after careful assessment.

Nitrofurantoin is however contraindicated in infants under three months of age and in pregnant women during labour and delivery, because of the possible risk of haemolysis of the infants' immature red cells.

Breast-feeding

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.

4.7. Effects on ability to drive and use machines

Nitrofurantoin may cause dizziness and drowsiness and the patient should not drive or operate machinery if affected this way.

4.8. Undesirable effects

Respiratory

If any of the following respiratory reactions occur the drug should be discontinued.

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.

Chronic pulmonary reactions occur rarely in patients who have received continuous therapy for six months or longer and are more common in elderly patients. Changes in ECG have occurred, associated with pulmonary reactions.

Minor symptoms such as fever, chills, cough and dyspnoea may be significant. Collapse and cyanosis have been reported rarely. 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. Pulmonary function may be impaired permanently, even after cessation of therapy.

Hepatic

Hepatic reactions including cholestatic jaundice and chronic active hepatitis, occur rarely. Fatalities have been reported. 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). The onset may be insidious. Treatment should be stopped at the first sign of hepatotoxicity.

Neurological

Peripheral neuropathy (including optical neuritis) with symptoms of sensory as well as motor involvement, which may become severe or irreversible, has been reported infrequently. Less frequent reactions of unknown causal relationship are depression, euphoria, confusion, psychotic reactions, nystagmus, vertigo,

dizziness, asthenia, headache and drowsiness. Treatment should be stopped at the first sign of neurological involvement.

Gastrointestinal

Nausea and anorexia have been reported. Emesis, abdominal pain and diarrhoea are less common gastrointestinal reactions.

Haematological

Agranulocytosis, leucopenia, granulocytopenia, haemolytic anaemia, thrombocytopenia, megaloblastic anaemia, glucose-6-phosphate dehydrogenase deficiency anaemia, and eosinophilia have been reported. Aplastic anaemia has been reported rarely. Cessation of therapy has generally returned the blood picture to normal.

Hypersensitivity

Allergic skin reactions manifesting as angioneurotic oedema, maculopapular, erythematous or eczematous eruptions, urticaria, rash, and pruritus have occurred.

Lupus-like syndrome associated with pulmonary reaction to nitrofurantoin has been reported.

Exfoliative dermatitis and erythema multiforme (including Stevens-Johnson Syndrome) have been reported rarely.

Other hypersensitivity reactions include anaphylaxis, sialadenitis, pancreatitis, drug fever, and arthralgia.

Miscellaneous

Transient alopecia and benign intracranial hypertension.

As with other antimicrobial agents, superinfections by fungi or resistant organisms such as *Pseudomonas* may occur.

However, these are limited to the genito-urinary tract because suppression of normal bacterial flora does not occur elsewhere in the body.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9. Overdose

Symptoms and signs of overdosage include gastric irritation, nausea and vomiting. There is no known specific antidote. Nitrofurantoin can be haemodialysed. Standard treatment is by induction of emesis or by gastric lavage in cases of recent ingestion. Monitoring of full blood count, liver function tests and pulmonary function, are recommended. A high fluid intake should be maintained to promote urinary excretion of the drug.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, nitrofurantoin derivatives

ATC code: J01XE01

Mechanism of action

Nitrofurantoin is a broad spectrum antibacterial agent, active against the majority of urinary pathogens. The wide range of organisms sensitive to the bactericidal activity include:

Escherichia coli

Enterococcus Faecalis

Klebsiella Species

Enterobacter Species

Staphylococcus Species, e.g. S.Aureus, S.Saprophyticus, S.Epidermidis

Citrobacter Species

Clinically most common urinary pathogens are sensitive to Nitrofurantoin.

Most strains of proteus and serratia are resistant. All pseudomonas strains are resistant.

5.2. Pharmacokinetic properties

Orally administered nitrofurantoin is readily absorbed in the upper gastrointestinal tract and is rapidly excreted in the urine. Blood concentrations at therapeutic dosages are usually low with an elimination half-life of about 30 minutes.

Maximum urinary excretion usually occurs 2-4 hours after administration of nitrofurantoin. Urinary drug dose recoveries of about 40-45% are obtained.

5.3 Preclinical safety data

Carcinogenic effect of nitrofurantoin in animal studies was observed. However, human data and extensive use of nitrofurantoin over 50 years do not support such suggestion.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

- Lactose monohydrate
- Sodium lauryl sulphate
- Colloidal silica
- Magnesium stearate

6.2. Incompatibilities

There are no known incompatibilities.

6.3. Shelf life

2 years.

6.4. Special precautions for storage

NIFURAN capsules should be stored at 25°C in the original container, away from children!
There are no special storage requirement of the drug.

6.5. Nature and contents of container

Cardboard box with 30 capsules of 50 mg of nitrofurantoin in the blister pack (3 blisters x 10 capsules)

6.6. Special precaution for disposal of unused medicine products - enviremental risk

The process of unused medicines and waste materials obtained from these drugs is carried out according to the regulations for the handling and disposal of pharmaceutical waste.

7. Classificatio

- Prescription only.

8. MARKETING AUTHORIZATION HOLDER

ZADA Pharmaceuticals Ltd.,
Donji Bistarac, 75300 Lukavac, Bosnia & Herzegovina.

9. MARKETING AUTHORISATION NUMBER

04-07.3-2-2409/16

10. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26.04.2017.

11. DATA OF LAST/PARTIAL REVISION OF THE TEXT

April, 2017.

Amela Hrnjić, MD