1. NAME OF THE MEDICINAL PRODUCT

Furadonin 100 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: nitrofurantoin (Nitrofurantoinum).
Each tablet contains 100 mg nitrofurantoin monohydrate (Nitrofurantoinum monohydricum).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets
Round, flat yellow or yellow-green tablet with bevelled edge and slightly uneven colour of the tablets surface.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of acute uncomplicated and severe chronic recurrent lower urinary tract infections, caused by susceptible bacteria.
For the prophylaxis against urinary tract infections.

4.2 Posology and method of administration

Posology

*Acute uncomplicated urinary tract infections*
Adults: 100mg two times daily for seven days
Children over 12 years of age may use the adult doses.

*Severe chronic recurrent urinary tract infections*
Adults: 100mg 3 to 4 times per day for seven days
Dose reduction or nitrofurantoin withdrawal may be required in case of nausea.

*Prophylaxis against urinary tract infections*
Adults: 100 mg before bedtime.

There is no data on the doses of Furadonin in patients with hepatic and/or renal impairment and elderly patients (see section 4.3).

*Children under 12 years of age*
Not suitable for children under 12 years of age, due to nitrofurantoin dose in one tablet. A more suitable dosage form, containing a smaller amount of nitrofurantoin is recommended for this age group.

*The recommended doses for children and infants over three months of age*
*For the treatment of urinary tract infections:* 3mg/kg body weight a day in four divided doses.
*For the prophylaxis against urinary tract infections:* 1mg/kg body weight once a day before bedtime.
Method of administration

To be taken with or shortly after meals with a sufficient amount of water.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1; Anuria, oliguria; Renal failure (creatinine clearance of less than 60 ml/min); Glucose-6-phosphate dehydrogenase deficiency; Porphyria; Neuritis, polyneuropathy, lung fibrosis; Pregnancy and lactation; Children under 12 years of age (for 100 mg tablets). Nitrofurantoin is not recommended for the treatment of pyelonephritis, which is combined with renal parenchymal inflammation or perirenal abscess.

4.4 Special warnings and precautions for use

Caution should be exercised in patients with anaemia, vitamin B (particularly folate) deficiency, electrolyte imbalance, pulmonary conditions, diabetes mellitus, hepatic impairment and susceptibility to peripheral neuropathy. Therapy should be discontinued at the first signs of neuropathy.

Nitrofurantoin should be used with caution in patients with impaired renal function. Due to the decreased nitrofurantoin excretion in the urine, the antimicrobial urine concentration may not be achieved, resulting in nitrofurantoin high plasma concentrations and toxicity risk (The medicinal product is contraindicated if creatinine clearance <60 ml/min).

No significant differences in treatment responses are identified between the elderly (above 65 years of age) and younger patients, however caution is advisable due to the possible renal function impairment.

Close monitoring of the pulmonary condition of patients receiving long-term therapy is warranted (especially in the elderly). Pulmonary reactions are more possible in elderly patients. Therapy should be stopped at the first appearance of lung damage symptoms.

Blood count and liver function parameters should be monitored particularly in case of long-term use. Cholestatic jaundice and chronic hepatitis were reported.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including nitrofuran derivatives. There have been reports of pseudomembranous colitis with the use of nitrofurantoin. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea caused by suppression of intestinal microflora during or subsequent to the administration of any antibacterial agents. In case of mild severity of pseudomembranous colitis usually discontinuation of antimicrobial agent is enough. In case of moderate to severe pseudomembranous colitis an appropriate therapy should immediately be initiated.

In case of reduced susceptibility to nitrofurantoin the medicinal product should be discontinued and other antibacterial agent chosen.

Interaction with laboratory test results

The administration of Furadonin may result in a false-positive reaction for glucose in the urine using a copper reduction method. It is recommended that glucose tests based on enzymatic glucose oxidase reaction be used.

Nitrofurantoin may impart a brown colour to the urine.
4.5 Interaction with other medicinal products and other forms of interaction

Antacids and adsorbents, when administered concomitantly with nitrofurantoin, reduce both the rate and extent of absorption. Concomitant administration should be avoided.

Uricosuric drugs, such as probenecid and sulfipyrazone, can inhibit renal excretion of nitrofurantoin, therefore, increasing nitrofurantoin serum levels that may result in decreased efficacy and increased toxicity risk. Concomitant administration is not recommended.

There are evidence of antibacterial antagonism between quinolones and nitrofurans (nalidixic acid, fluoroquinolones) in vitro. However, in vivo clinical significance of this interaction has not been established, therefore, concomitant administration should be avoided.

The consumption of alcoholic beverages during therapy should be avoided. Co-administration may cause undesirable effects.

4.6 Fertility, pregnancy and lactation

Pregnancy
Furadonin is contraindicated during pregnancy. Nitrofurantoin readily crosses the placenta. Animal studies with nitrofurantoin have revealed high-dose toxicity.

Lactation
Furadonin is contraindicated during lactation. Nitrofurantoin soluble is excreted into human breast milk. Even negligible nitrofurantoin quantity may cause haemolytic anaemia in infants.

4.7 Effects on ability to drive and use machines

Furadonin has no or negligible influence on the ability to drive and use machines. If patients taking Furadonin suffer from dizziness, headache or other central nervous system disorders, caution should be exercised.

4.8 Undesirable effects

Like all medicines Furadonin can cause side effects, although not everybody gets them. Their frequency is defined using the following conventions: very common (≥1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Infections and infestations: there have been sporadic reports of pseudomembranous colitis with the use of nitrofurantoin. In case of mild severity of pseudomembranous colitis usually discontinuation of antimicrobial agent is enough. In case of moderate to severe pseudomembranous colitis an appropriate therapy should immediately be initiated.

Blood and lymphatic system disorders: rare – in patients with glucose-6-phosphate dehydrogenase deficiency megaloblastic anaemia may occur, thrombocytopenia, granulocytopenia or agranulocytosis, leucopenia, haemolytic anaemia.

Immune system disorders: in rare cases autoimmune reactions mainly associated with chronic changes in the lungs and liver have been reported. This Lupus-like syndrome manifests as fever, short-term exanthema, arthralgia and eosinophilia. High serum values of more than 2 of the following characteristics: antinuclear antibodies, antibodies against smooth muscle system or glomerular basement membrane and Coombs's test are present.

Nervous system disorders: common – headache; rare – benign intracranial hypertension; peripheral neuropathy with symptoms of paresthesia, burning sensation of extremities, muscle weakness. The medicinal product should be discontinued at the first appearance of peripheral neuropathy symptoms (see section 4.4).

Respiratory, thoracic and mediastinal disorders: acute and chronic pulmonary reactions are commonly manifested by fever, cough, chest pain, dyspnoea and eosinophilia. Pulmonary infiltration with consolidation or pleural effusion may occur within a few hours or days of treatment and are usually reversible with cessation of therapy. Subacute and acute pulmonary reactions including lung fibrosis can develop unnoticed.
in patients during continuous therapy. Pulmonary fibrosis may be irreversible, especially if therapy is continued after the onset of symptoms. Nitrofurantoin should be discontinued at the first appearance of pulmonary reactions and appropriate therapy should be applied.

Gastrointestinal disorders: common – nausea, vomiting, anorexia, frequency and severity of which is dose dependent. Rare – diarrhoea, pancreatitis. These undesirable effects may be minimised by taking Furaldin with food and sufficient amount of fluid.

Hepatobiliary disorders: rare – hepatitis, cholestatic jaundice (dose-independent, disappears after cessation of the therapy).

Skin and subcutaneous tissue disorders: common – hypersensitivity reactions including rash, urticarial, itching; rare – alopecia reversible. In some cases – angioedema, salivary glands inflammation, exfoliative dermatitis, erythema multiforme, Lupus-like syndrome.

Reproductive system and breast disorders: in very rare cases, transient spermatogenesis disorders are observed.

4.9 Overdose

Symptoms: nausea, vomiting, headache and dizziness. Nervous system disorders point to the increased nitrofurantoin blood plasma concentrations. Polyneuritis may develop as a result to the cumulation of nitrofurantoin and its metabolites, thus, the risk of polyneuritis increases in case of renal impairment.

Treatment: a high fluid intake should be maintained to promote urinary excretion of the medicinal product. In cases of recent ingestion, gastric lavage should be considered. Nitrofurantoin is dialyzable. There is no known specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, nitrofuran derivatives.
ATC code: J01XE01

Nitrofurantoin is an antibacterial agent, synthetic nitrofuran derivative, active against the majority of urinary pathogens. The exact mechanism of action has not been fully elucidated. It is considered that the mechanism of action is based on the ability to inhibit various microbial enzyme systems. Nitrofurantoin is bacteriostatic at low doses and bactericidal at high doses. Nitrofurantoin efficacy in the treatment of urinary tract infections is dependent on high concentrations in the urine, as nitrofurantoin bactericidal concentrations are achieved only in urinary tract. The medicinal product is ineffective in case of systemic bacterial infections, since nitrofurantoin bacteriostatic concentrations in the blood and tissues cannot be achieved due to the rapid renal elimination.

Nitrofurantoin is active against the majority of urinary pathogens. The wide range of organisms sensitive to the bactericidal activity include: Enterococcus Species, Escherichia coli, Citrobacter Species, group B streptococci, Staphylococcus aureus, Streptococcus epidermidis, as well as rare urinary pathogens Salmonella Species, Bacteroides Species, Streptococcus pneumonia.

Moderately susceptible species: Klebsiella pneumonia, Enterobacter Species.
Species for which resistance may be a problem: most strains of Proteus species or Serratia species. Nitrofurantoin has no activity against Pseudomonas aeruginosa, Pseudomonas cepacia, Providencia Species, Acinetobacter Species.

Nitrofurantoin is not recommended for the treatment of pyelonephritis or renal parenchymal inflammation, as well as urinary tract infections caused by strains of Gonococci, Chlamydia or Mycoplasma.

Development of resistance to nitrofurantoin is not significant, but it is possible in case of prolonged therapy. Cross-resistance with other antibacterial agent, excluding nitrofuran derivatives, has not been observed.

5.2 Pharmacokinetic properties

Amantadine is well absorbed from the gastrointestinal tract. Bioavailability of nitrofurantoin is approximately 50%. Concomitant intake of food increase nitrofurantoin bioavailability.
The active substance is 20 to 60% plasma protein bound. Therapeutic concentrations in plasma and organism tissues are not reached. 20 – 44% of a dose eliminated unchanged in the urine, as a result nitrofurantoin possesses bacteriostatic and bactericidal activity in case of urinary tract infections. Following single dose administration of 100 mg peak urine concentrations (50-150 µg/ml) attained in the urine within 30 minutes. In adults with normal renal function nitrofurantoin elimination half-life is 25 to 30 minutes. Nitrofurantoin concentration in the urine decreases progressively, therapeutic concentrations remain for 8 to 10 hours. Nitrofurantoin biotransformation occurs in the liver. Approximately 50% of a single dose of nitrofurantoin is recovered unchanged from the urine over 24 hours and about 50% - as inactive metabolites. Plasma concentrations are higher and half-life prolonged in patients with renal impairment. Therapeutic concentrations of nitrofurantoin may not be attained in the urine of patients with creatinine clearance of less than 60 ml/min; cumulation of the active substance and increased risk of toxicity are possible. In these patients use of nitrofurantoin is not recommended.

Nitrofurantoin is more active in the acidic urine. If the urine pH is above 8, nitrofurantoin loses its bactericidal activity.

Nitrofurantoin crosses the placenta and is detected in trace amounts in breast milk.

5.3 Preclinical safety data

Acute toxicity. After oral administration of nitrofurantoin LD50 in mice is 360 mg/kg, in rats – 604 mg/kg body weight. Carcinogenicity. Studies in animals implied that nitrofurantoin may be carcinogenic, but the results were insufficiently convincing and carcinogenic activity was not found in humans. Teratogenicity. Non-clinical standardized studies revealed teratogenicity when nitrofurantoin was used in doses exceeding maximum human dose and over an extended period of time.

High doses of nitrofurantoin in rats caused a break in spermatogenesis, which was reversible after nitrofurantoin discontinuation. Dose of 10 mg/kg per day and more, in some cases, in healthy men may result in mild to moderately severe spermatogenesis disorders with spermatozoon count decrease.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potato starch, silica, calcium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25 °C. Protect from light and moisture.

6.5 Nature and contents of container

10 tablets in a opaque (white) polyvinyl chloride (PVC) film and aluminium foil blister. 2 blisters (20 tablets) and the package leaflet in a carton pack.

6.6 Special precautions for disposal

No special requirements.
7. MARKETING AUTHORISATION HOLDER

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10. DATE OF REVISION OF THE TEXT

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