SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Uvamin™ 100 mg retard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance

Each Uvamin™ 100 mg retard capsule contains: nitrofurantoin 100 mg.

Excipients
Colouring agent: E104; excipients for capsule (for a full list of excipients, see section 6.1.)
Each capsule contains lactose monohydrate 20 mg per capsule.

3. PHARMACEUTICAL FORM

Hard gelatin capsule, size No 2.
Uvamin™ 100 mg retard hard capsule has yellow cap and body with the imprint “100”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.
Official recommendations on the appropriate use of antibiotics should be followed, particularly recommendations for use regarding the prevention of increased antibiotic resistance.

4.2 Posology and method of administration

Adults
Acute urinary tract infections
One Uvamin™ 100 mg retard capsule 2-3 times daily for 7-10 days.

Chronic urinary tract infections (long-term treatment)
One Uvamin™ 100 mg retard capsule 1-2 times daily for several weeks or months.

Children
Uvamin™ 100 mg retard is not recommended for use in children under 12 years.

Elderly
No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 60 mL/min. See precaution and risks to elderly patients associated with long-term therapy (see section 4.4).

Renal impairment
Nitrofurantoin should be administered only if renal function is normal (creatinine clearance values over 60 ml/min) and when lower-risk antibiotics and chemotherapeutic agents cannot be employed (see sections 4.3 and 4.4).

Hepatic impairment
No dose adjustment is necessary in patients with hepatic function disorders. See special warnings and precautions for use (see section 4.4).

Method of administration
For oral administration.
To improve tolerability, nitrofurantoin should be taken during or immediately after meals with sufficient liquid.

4.3 Contraindications

Nitrofurantoin is contraindicated:

- in patients with known hypersensitivity to nitrofurantoin, other nitrofurans or to any of the excipients
- in patients with renal dysfunction with creatinine clearance below 60 ml/min or with elevated plasma creatinine levels
- in cases of glucose-6-phosphate dehydrogenase deficiency (see “Pregnancy/Lactation”)
- in cases of acute porphyria
- in infants under 3 months of age and in the final stages of pregnancy (during labour and delivery), due to the theoretical possibility of haemolytic anaemia in the foetus or neonate (under 3 months) resulting from the immature red blood cell enzyme system
- Oliguria, anuria. Polyneuropathy, neuritis. Pulmonary fibrosis.

4.4 Special warnings and precautions for use

Nitrofurantoin should be administered only if renal function is normal (creatinine clearance values over 60 ml/min) and when lower-risk antibiotics and chemotherapeutic agents cannot be employed.
The utmost caution is advised in patients with impaired renal excretion, since insufficient elimination can lead to accumulation whilst, at the same time, the urinary active substance concentration may be significantly reduced.
During long-term therapy, the patient’s pulmonary function must be monitored regularly (especially in the case of elderly patients). Early detection of nitrofurantoin-induced pulmonary hypersensitivity reactions and, if necessary, immediate discontinuation of nitrofurantoin treatment are important in impeding progression and avoiding potentially irreversible damage.
Chronic pulmonary reactions (including pulmonary fibrosis and diffuse interstitial pneumonia) can develop unnoticed and are common in elderly patients.
In recurrent or severe cases, a surgical basis for the infection should be ruled out.
As pre-existing conditions can mask side effects affecting the lungs or liver, nitrofurantoin should be used with caution in patients with pulmonary diseases, hepatic function disorders, neurological conditions and allergic diathesis.
Peripheral neuropathy and susceptibility to peripheral neuropathy, which can become severe or irreversible, have been observed and can become life-threatening. Treatment should be discontinued at the first signs of nerve involvement (paraesthesia).
Caution is advised in cases of anaemia, diabetes mellitus, electrolyte imbalances, paresis and vitamin B deficiency (especially folate deficiency), as the risk of peripheral neuropathy is increased in such cases. Nitrofurantoin should be immediately stopped at the first signs of tingling or numbness in the extremities.
Patients should be monitored closely for signs of hepatitis (especially during relatively long-term administration).
The urine may turn yellow or brown after nitrofurantoin administration.
False positive urinary glucose test results may occur in patients treated with nitrofurantoin, if the test detects reducing substances in the urine.
Nitrofurantoin must be discontinued at the first signs of haemolysis in patients with suspected glucose-6-phosphate dehydrogenase deficiency.

Gastrointestinal reactions can be reduced by taking the medication with food or milk, or by adapting the dose.
During long-term therapy the patient must be monitored closely for the occurrence of hepatic or pulmonary symptoms or other evidence of toxicity.
Monitoring of the blood count, renal function and hepatic function, together with neurological examinations, are essential during prolonged therapy.
Nitrofurantoin must be discontinued if pulmonary, hepatic, haematological or neurological syndromes that cannot be otherwise explained should occur.
Nitrofurantoin is not indicated for urinary tract infections which may be accompanied by parenchymal involvement and/or bacteraemia (pyelonephritis, acute cystitis in men), or in cases of urethritis (usually caused by gonococci, *Chlamydia* and/or *Mycoplasma*) or prostatitis (inadequate penetration of nitrofurantoin into the prostate secretion).
Upon administration of nitrofurantoin, proliferation of resistant microorganisms (especially *Pseudomonas*) can occur. Appropriate treatment must be instituted at the onset of such superinfections.
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

Nitrofurantoin antagonises the activity of nalidixic acid and other gyrase inhibitors in vitro but the clinical relevance of this interaction is unclear.
Nitrofurantoin can lower the plasma concentrations of phenytoin, thereby possibly reducing the efficacy of phenytoin.
Propantheline increases the urinary concentration of nitrofurantoin, probably as a result of improved absorption due to inhibition of gastric emptying.
Co-administration of sulphinpyrazone or probenecid can lead to the inhibition of renal excretion and hence to decreased activity and increased toxicity of nitrofurantoin.
Magnesium trisilicate antacids can decrease nitrofurantoin absorption and should therefore not be administered concurrently, but at least 1 hour later.
The effect of nitrofurantoin is decreased by interaction with sodium bicarbonate, sodium lactate and other urine-alkalising agents.
The antibacterial effect is reduced by carbonic anhydrase inhibitors and alkalisation of the urine.
Interaction with certain urinary glucose tests.
As nitrofurantoin belongs to the group of antibacterial agents, the following interactions are to be expected:

- Oestrogens: As with other antibiotics, nitrofurantoin can compromise the intestinal flora, which leads to lower absorption of oestrogens and reduced effectiveness of oestrogen-containing contraceptives. Therefore, female patients must be warned appropriately and additional contraceptive precautions must be used.
- The oral typhus vaccine is inactivated by antibacterial agents.

Interference with diagnostic methods
Nitrofurantoin gives false-positive results in the sugar test with copper sulphate solution (Benedict's reagent, Clinitest). Glucose oxidase methods are not affected (Clinistix, Tes-tape).
Possible yellowing/browning of the urine can result in too high or false-positive laboratory values (bilirubin, BUN).

4.6 Fertility, Pregnancy and lactation

Pregnancy
There are no adequate data available on the use of nitrofurantoin in pregnant women. Studies in animals have shown reproductive toxicity (see “Preclinical data”).
Use is contraindicated in the third trimester of pregnancy (risk of haemolytic anaemia in the neonate).
Uvamin™ 100 mg retard should not be used during the first 6 months of pregnancy unless clearly necessary.
Due to the potential risk of haemolysis of immature red blood cells in the neonate, nitrofurantoin is, however, contraindicated in babies under 3 months of age and in the final stages of pregnancy (during labour and delivery).

Breastfeeding
The breast-feeding of babies suspected or known to be suffering from red blood cell enzyme deficiency (including G6PD deficiency) must be avoided as traces of nitrofurantoin are detected in human milk.

4.7 Effects on ability to drive and use machines

Even when used as directed, this medicinal product may alter the reactions to such an extent that the ability to drive and use machines is impaired. This applies all the more in combination with alcohol.

4.8 Undesirable effects

Adverse reactions in Table 1 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: 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), unknown (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Tabulated list of adverse reactions

Table 1

Blood and lymphatic system disorders *Rare:* agranulocytosis, eosinophilia, leukopenia, granulocytopenia, haemolytic anaemia, glucose-6-phosphate dehydrogenase deficiency, thrombocytopenia and megaloblastic anaemia. Aplastic anaemia. The blood count generally returned to normal after discontinuation of treatment.
Immune system disorders *Rare:* exfoliative dermatitis and erythema multiforme (including Stevens-Johnson syndrome). Lyell's syndrome, anaphylactic shock after nitrofurantoin, autoimmune reactions after nitrofurantoin, usually in association with chronic pulmonary or hepatic reactions. Allergic skin reactions such as maculopapular, erythematous or eczematous rashes, urticaria, rash, angioedema and pruritus. *Unknown:* lupus-like syndrome, which is associated with pulmonary reactions to nitrofurantoin. Other hypersensitivity reactions include anaphylaxis, drug fever and arthralgias.

Nervous system disorders

Uncommon: peripheral neuropathy (including optic neuritis) with sensory and motor symptoms that can become severe or irreversible.
Less common reactions of unknown aetiology: depression, euphoria, confusion, psychotic reactions, nystagmus, dizziness, asthenia, headache and somnolence. Treatment must be discontinued at the first sign of neurological effects.
Unknown: benign intracranial hypertension.

Respiratory, thoracic and mediastinal disorders

Treatment with Uvamin™ 100 retard must be discontinued if any of the following respiratory reactions occur.
Uncommon: allergic pulmonary infiltration (called nitrofurantoin pneumonia) with episodes of coughing, dyspnoea and retrosternal pain may rarely lead to irreversible pulmonary fibrosis, particularly during long-term therapy.
A differentiation is made between acute, subacute and chronic forms of pulmonary reactions.
The acute form occurs with clinical symptoms of allergic pulmonary oedema, with sudden dyspnoea, coughing, fever and, notably, pulmonary infiltration (nitrofurantoin pneumonia), generally appearing some hours after the last nitrofurantoin dose. Upon discontinuation of the product, such syndromes resolve within 2-3 weeks.
The subacute form, 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.

Gastrointestinal disorders

Uncommon: vomiting, abdominal pain and diarrhoea.
Rare: pancreatitis.
Unknown: nausea and anorexia.

Hepatobiliary disorders

Rare: hepatic reactions, cholestatic jaundice and chronic active hepatitis including cases of death have been reported. Cholestatic jaundice is normally associated with short treatments (of up to 2 weeks). Chronic active hepatitis occasionally leading to hepatic necrosis is usually associated with long-term treatments (of over 6 months); it can begin insidiously and initially be unnoticed. Treatment must be discontinued at the first sign of hepatotoxicity.

Skin and subcutaneous tissue disorders

Rare: erythema nodosum and temporary hair loss.

Renal and urinary disorders

Rare: crystalluria.

Reproductive system and breast disorders

Rare: reversible disorders of spermatogenesis due to epithelial damage to the convoluted seminiferous tubules.

General disorders and administration site conditions *Very rare:* Outbreaks of sweating, feeling of weakness, globus symptoms.
Infections and infestations *Unknown:* As with other antibiotics, additional infections are possible with fungi or resistant microorganisms such as *Pseudomonas*.

To reports any side effect(s):

- ***Saudi Arabia:***

The National Pharmacovigilance and Drug Safety Centre (NPC)
Fax: +966-11-205-7662
Call NPC at +966-11-2038222, Exts: 2317-2356-2353-2354-2334-2340.
Toll free phone: 8002490000
E-mail: npc.drug@sfda.gov.sa
Website: www.sfda.gov.sa/npc

Other GCC States:

Please contact the relevant competent authority

4.9 Overdose

An overdose can lead to an increase in undesirable effects such as nausea, vomiting, headache and dizziness.
In the event of acute intoxication, gastric lavage should be performed. If absorption has already taken place, nitrofurantoin can be removed by haemodialysis, if necessary.
Monitoring of blood count, hepatic function tests and pulmonary function is recommended. Fluid intake should be kept high to encourage urination.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

ATC code: J01XE01

Mechanism of action

Nitrofurantoin is an antibiotic with activity against most urinary tract pathogens. It acts as a bactericidal agent in the renal tissues and in the urinary tract. The spectrum of sensitive microorganisms includes: *Escherichia coli*,
Enterococcus faecalis,
Klebsiella species,
Enterobacter species,
Staphylococcus species (e.g. *S. aureus*, *S. saprophyticus*, *S. epidermidis*).
Citrobacter Species
Clinically, the most common urinary pathogens are nitrofurantoin-susceptible.

Certain strains of Enterobacter and Klebsiella are resistant. Nitrofurantoin is ineffective against most strains of *Proteus* species or *Serratia* species, as well as *Pseudomonas* species.
The detailed mechanism of action of nitrofurantoin is not precisely known. Its action is probably based on interference with various bacterial enzyme systems (interference with protein synthesis). At low concentrations, its mode of action is primarily bacteriostatic and, at higher concentrations, it is bactericidal against proliferating and dormant pathogens. Active antibacterial concentrations are reached only in the interior of the efferent urinary tract and not in the blood or other tissues.

In vitro sensitivity spectrum
Susceptible microorganisms (MIC_{90} <32 µg/ml)
Enterococci, *E. coli*, *Citrobacter* spp., *Streptococcus* group B, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Salmonella* spp., as well as *Bacteroides* spp. and *Streptococcus pneumoniae*, which, however, are rarely a cause of infections in the urinary tract system.

Partially or moderately susceptible microorganisms (MIC_{90} = 32-128 µg/ml)
Enterobacter spp., *Klebsiella pneumoniae*.

Resistant microorganisms (MIC_{90} >128 µg/ml)
Pseudomonas aeruginosa, *Proteus* spp., *Pseudomonas cepacia*, *Providencia* spp., *Serratia* spp., *Acinetobacter*.
It is recommended that a sensitivity test be carried out in infections caused by moderately susceptible microorganisms, so that possible resistance can be excluded.

Resistance/Cross-resistance
During therapy, resistance develops slowly and gradually. Certain strains of *Enterobacter* and *Klebsiella* are resistant, while *Acinetobacter*, *Providencia*, *Pseudomonas* and *Serratia* are generally always resistant.
Cross-resistance with other nitrofurans can occur; however, no cross-resistance with other antibacterial agents has been reported to date.

5.2 Pharmacokinetic properties

Absorption
Nitrofurantoin is rapidly and almost completely absorbed from the small intestine. The macrocrystalline form is released more slowly, with the result that high initial serum concentrations are avoided and gastric intolerability occurs less frequently than with the usual microcrystalline form. Therapeutically effective serum levels are not achieved with standard doses. After a single 100 mg dose of Uvamin™ 100 retard, the mean peak plasma concentration was 460 ng/ml. Peak urinary concentrations were between 13 and 88 ng/ml, which were reached in most cases after 2-6 hours.

Distribution
The volume of distribution is 0.3-0.7 l/kg and plasma protein binding is about 50-60%.
Nitrofurantoin crosses the placenta and is excreted in human milk.

Metabolism
The substance is metabolised rapidly in the body. About 40-50% is inactivated in the liver by glucuronidation and N-acetylation.

Elimination
Nitrofurantoin is excreted mainly via the renal route. About 40% of the administered dose appears unchanged in the urine. The remaining 60% is metabolised at various sites including the liver. 16.7% of nitrofurantoin is metabolised by glomerular filtration and 83.3% by tubular secretion. Reabsorption is dependent on the urinary pH. As a weak acid, nitrofurantoin undergoes non-ionic diffusion. With increasing urinary acidity, a significant fraction of the amount excreted proximally is reabsorbed in the distal nephron segments, whilst alkalinisation of the urine results in higher urinary concentrations of

nitrofurantoin. However, alkalinisation of the urine for the treatment of urinary tract infections is of little benefit, as the antibacterial efficacy of nitrofurantoin is reduced as a result. People with normal renal function have a serum half-life of only 20 minutes.

Kinetics in special patient groups
In patients with severely impaired renal function, nitrofurantoin accumulates in the serum with a plasma half-life of up to 1 hour. Nitrofurantoin is contraindicated in patients with a creatinine clearance of less than 60 ml/min due to the expected risk of accumulation and loss of efficacy.

5.3 Preclinical safety data

Mutagenesis
Nitrofurantoin induces point mutations in certain types of Salmonella typhimurium and forward mutations in L5178Y mouse lymphoma cells. Nitrofurantoin caused increased sister chromatid staining and chromosome aberrations in CHO cells, but not in human cell cultures.
Following administration of nitrofurantoin doses via the feed or injection, results of the Drosophila sex-linked recessive lethal assay were negative. Nitrofurantoin did not cause any hereditary mutations in laboratory rodents.

Carcinogenicity
Nitrofurantoin led to an increased incidence of tubular adenomas, benign mixed tumours and granulosa cell tumours of the mouse ovary. In one study, in which pregnant female mice were subcutaneously administered 75 mg/kg of nitrofurantoin, papillary adenomas of unknown severity were identified in the F1 generation. An increased incidence of abnormal renal tubular cell neoplasms, osteosarcomas and subcutaneous neoplasms was observed in male rats.

Reproductive toxicity
An increased malformation rate was observed in animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill: hypromellose, lactose monohydrate, cellulose microcrystalline, purified water.

Capsule shell: hard gelatin capsule shell, gelatine, quinoline yellow, titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 Months

6.4 Special precautions for storage

Do not store above 30 ºC.

6.5 Nature and contents of container

Uvamin 100 mg retard capsules are packed in PVC/PVDC – Aluminium blisters, which are packed in carton box.
Each pack contains 2 blisters each of 10 capsules.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Acino Pharma AG, Liesberg, Switzerland

8. MARKETING AUTHORISATION NUMBER

40-222-10

9. DATE OF FIRST AUTHORISATION

21/07/2010

10. DATE OF REVISION OF THE TEXT

11/2018