Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nitrofurantoin Kora Healthcare 50 mg capsule, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 50 mg capsule contains 50 mg of nitrofurantoin (in macrocrystalline form).

Excipient(s) with known effect
Each 50 mg capsule contains 103.5 mg of lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard (hard capsule)

50 mg: a size 3 hard gelatin capsule with a yellow cap and white body of approx. 16mm length and 6mm diameter, containing a yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nitrofurantoin Kora Healthcare is indicated in infections of the urinary tract that are caused by micro-organisms sensitive to nitrofurantoin (see section 5.1).

- In acute uncomplicated lower urinary tract infections;
- For short-term prophylaxis after surgical procedures, transurethral interventions, catheterization, cystoscopy and indwelling catheter;
- For long-term treatments of urinary tract infections up to 6 months; longer than 6 months only if the benefits clearly outweigh the potential risks. In view of the side effects, long-term therapy should only be used if no suitable alternative is available (see section 4.4).

Nitrofurantoin Kora Healthcare is indicated in adults and children (aged over 5 years).
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Treatment of acute uncomplicated lower urinary tract infections
Adults and children aged over 12 years: one 50 mg capsule 4 times a day.

General use: 5 to 7 days or at least 3 days after no infection is detectable in the urine.

In girls aged 5 to 12 years: the usual dose is 3 mg/kg body weight up to a maximum of 6 mg/kg body weight per day divided into 4 doses; for 7 days or at least 3 days after no infection is detectable in the urine.
This pharmaceutical form (capsules) may not be suitable for use in children in this age group.

Short-termprophylaxis for urinary tract surgery
Adults and children from 12 years of age: 50 mg 4 times per day on the day of surgery and for 3 days after.

Long-term treatment of urinary tract infections
Adults and children from 12 years: 50 to 100 mg once a day, usually in the evening before sleep.

Paediatric population
For the paediatric population consideration should be given to the use of other pharmaceutical forms, e.g. Nitrofurantoin Suspension

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
Patient with renal impairment will require renal function monitoring during treatment with nitrofurantoin. Dosage adjustments may be necessary in patients including the elderly with mild to moderate renal impairment (see section 4.3, 4.4 and 4.8).

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.

Nitrofurantoin must not be administered to patients with a creatine clearance < 45 ml/min (see section 4.3).

Hepatic impairment
Nitrofurantoin should be used with caution in patients with hepatic impairment especially elderly patients on long term nitrofurantoin therapy may require monitoring (see section 4.4).

Method of administration
For oral use.
This medicinal product should always be taken with food or milk. Taking Nitrofurantoin Kora Healthcare with a meal improves absorption and is important for optimal efficacy.

4.3 Contraindications

- Hypersensitivity to the active substance, other nitrofurans or to any of the excipients listed in section 6.1
- Patients with renal impairment (eGFR below 45 ml/min)
- G6PD deficiency
- Acute porphyria
- In infants under three months of age as well as pregnant women at term (during labour and delivery) because of the theoretical possibility of haemolytic anaemia in the foetus or in the newborn due to immature erythrocyte enzyme systems
- Patients who have previously had a lung or liver reaction other than a peripheral neuropathy after use of nitrofurantoin or other nitrofurans.

4.4 Special warnings and precautions for use

Prolonged use of Nitrofurantoin Kora Healthcare is not recommended. During nitrofurantoin treatment there may be lung and liver complications that could be life-threatening (see section 4.8). If this happens treatment should be stopped immediately and the necessary measures should be taken.

Pulmonary reactions

Acute, subacute and chronic pulmonary reactions have been observed in patients treated with nitrofurantoin. If these reactions occur, nitrofurantoin must 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 conditions of patients receiving long-term therapy is warranted (especially in the elderly).

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.

Existing conditions can mask pulmonary and hepatic side effects. Caution should be exercised when nitrofurantoin is used in patients with pulmonary diseases, disturbed hepatic function, neurological disorders and allergic diathesis.

Neuropathy
Peripheral neuropathy, which can become serious or irreversible, has occurred (usually within two months) and can become life-threatening. Therefore, treatment should be discontinued at the first signs of neural involvement (paraesthesia, weakness). Conditions such as renal insufficiency, anaemia, diabetes mellitus, alcoholism, electrolyte disorder, vitamin B deficiency (especially folate deficiency) and exhaustive conditions increase the risk of developing peripheral neuropathy.

Laboratory tests
Urine can be coloured yellow or brown after taking nitrofurantoin. Patients taking nitrofurantoin can test false positive for urine glucose (if tested for urine reducing substances).
Nitrofurantoin may affect certain laboratory tests. False-positive results or incorrectly high readings can occur with urinary glucose tests that rely on copper sulphate reduction, such as Benedict's reagent and Clinitest (Ames). However, there is no interference with the Clinistix test.

Haematologic effects
Nitrofurantoin Kora Healthcare should be discontinued if there is evidence of haemolysis in suspected persons of glucose-6-phosphate dehydrogenase deficiency (ten percent of individuals with dark skin colour of Afro-Caribbean origin and a small percentage of ethnic groups coming from the Mediterranean, Middle Eastern or Western Asian origin suffer from a G6PD deficiency).

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

4.5 Interaction with other medicinal products and other forms of interaction

The effect of other medicinal products on nitrofurantoin:

- Food or medicinal products that delays gastric emptying increase the bioavailability of nitrofurantoin, probably due to better dissolution in the gastric juice.
- Carbonic anhydrase inhibitors and alkalising agents can reduce the antibacterial activity of nitrofurantoin.
- Magnesium trisilicate co-administered with nitrofurantoin reduces the absorption of nitrofurantoin.
- There may be an antagonism between quinolones and nitrofurantoin: simultaneous application is not recommended.
- Probenecid and sulfinpyrazone can reduce the renal clearance of nitrofurantoin.

As Nitrofurantoin belongs to the group of antibacterials it will have the following resulting interactions:

- Typhoid fever vaccine (oral): antibacterial agents make the oral typhoid fever vaccine ineffective.

4.6 Fertility, pregnancy and lactation

Pregnancy
A large amount of data in pregnant women has no teratogenicity or foetal/neonatal toxicity. Animal studies have shown toxic effects (see section 5.3). If prescribed by a doctor, nitrofurantoin can be used during pregnancy.

However, nitrofurantoin is contraindicated in in pregnant women during labour and delivery, because of the possible risk of haemolysis of the infants' immature red cells., see section 4.3.

Breast-feeding
Nitrofurantoin is detected in trace amounts in breast milk. Nitrofurantoin can be used during breastfeeding. Avoid breast feeding an infant younger than one month, or an infant known or suspected to have any erythrocyte enzyme deficiency (including G6PD deficiency).

Fertility
In men, a temporary stoppage in spermatogenesis and reduced sperm counts were observed at supratherapeutic doses. Clinical doses are not associated with male infertility. No reduced fertility was observed in animal studies. In rats, at high doses observed a temporary stoppage in spermatogenesis.

4.7 Effects on ability to drive and use machines

Nitrofurantoin may cause dizziness and drowsiness. If this happens the patient should not drive or operate machinery until the symptoms disappear.

4.8 Undesirable effects

Reported adverse reactions for nitrofurantoin are listed below according to organ system class.
The frequency of the adverse reactions listed below is defined according to the following convention: very common (≥1/10), rare (≥1/10,000 to <1/1,000), not known (frequency cannot be estimated from the available data).

System Organ Class	Very common	Rare	Not known
Infections and infestations			Sialadenitis.
Blood and lymphatic system disorders		Agranulocytosis, eosinophilia, leucopenia, granulocytopenia, thrombocytopenia, aplastic anaemia and megaloblastic anaemia[1]	
Immune system disorders		Exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome	Maculo-papular rash, rash erythematous, eczema, urticaria, angioedema. Lupus syndrome (associated with lung reactions), anaphylactic reactions, DRESS syndrome, cutaneous vasculitis
Metabolism and nutrition disorders		Anorexia	
Psychiatric disorders [2]			Depression, euphoria, confusion, psychotic reactions, headaches[2]**.**
Nervous system disorders	Idiopathic intracranial hypertension		Peripheral motor neuropathy,peripheral sensory neuropathy. Neuritis optics. Nystagmus, dizziness, somnolence
Cardiac disorders		Circulatory collapse and cyanosis.	
Respiratory, thoracic and mediastinal disorders			Acute lung injury[3] manifested by fever, chills[4], chest pain, dyspnoea, cough, lung infiltration with consolidation or pleural effusion[5] and eosinophilia Subacute respiratory reactions manifested by fever and eosinophilia Chronic lung reactions manifested by fever, chills, cough and dyspnoea[6]
Gastrointestinal disorders		Nausea.	Vomiting, abdominal pain, diarrhoea, pancreatitis
Hepatobiliary disorders		Cholestatic icterus and chronic hepatitis[7].	Autoimmune hepatitis
Skin and	Short-lived		Cutaneous vasculitis

subcutaneous tissue disorders	alopecia		
Renal and urinary disorders	Superinfections by fungi or resistant organisms (i.e. Pseudomonas)		Nephritis interstitial
Congenital, familial and genetic disorders		Haemolytic anaemia/G6PD deficiency	
General disorders and administration site conditions			Asthenia, arthralgia

[1] Treatment should be discontinued until the blood count returns to normal.
[2] Treatment should be discontinued at the first signs of neurological and/or psychological involvement.
[3] If any of the following respiratory reactions occur, the use of this medicinal product should be stopped.
[4] Acute pulmonary reactions usually occur within the first week of treatment and are reversible after discontinuation of treatment.
[5] Demonstrated through X-ray diagnosis.
[6] Chronic pulmonary reactions are rare in patients receiving continuous treatment for 6 months or more get longer and are more common in older patients.
[7] Fatalities are reported. Cholestatic icterus is generally associated with short-term treatment (usually up to 2 weeks). Chronic active hepatitis, which occasionally leads to necrosis, is generally associated with long-term treatment (usually 6 months). Treatment should be discontinued at the first signs of hepatotoxicity. See section 4.4.

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. Healthcare professionals are asked to report any suspected adverse reactions via
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Symptoms
Symptoms and signs of overdose include gastric irritation, nausea and vomiting.

Management
There is no known specific antidote. However, nitrofurantoin can be haemodialysed in cases of recent ingestion. Standard treatment is by induction of emesis or by gastric lavage within one hour after ingestion. Monitoring of full blood count, liver function and pulmonary function tests are recommended. A high fluid intake should be maintained to promote urinary excretion of this drug.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, other antibacterials, nitrofuran derivatives

ATC code: J01XE01

Mechanism of action
Nitrofurantoin belongs to the nitrofurans. Therapeutically active concentrations are only achieved in the urine. Nitrofurantoin is most active in acidic urine and if the pH value is higher than 8 the majority of the antibacterial activity is lost. The exact mechanism of action is not known. Multiple working mechanisms are described. Nitrofurantoin inhibits a number of bacterial enzymes. It also inhibits bacterial ribosomal proteins and thus causes a complete inhibition of bacterial protein synthesis.

It is possible that nitrofurantoin also causes damage to the DNA.

Resistance
Resistance rarely develops during treatment with nitrofurantoin, possibly because nitrofurantoin has different mechanisms of action. Resistance can occur with long-term treatment. Plasmid-encoded resistance is reported in *Escherichia coli*. Reduced sensitivity has been observed among ESBL- producing intestinal bacteria. Resistance can be due to the loss of nitrofuran reductases that generate the active intermediates.

Breakpoints
The following breakpoints have been determined by EUCAST:

Aerococcus sanguinicola and A. urinae (uncomplicated UTI only)	S≤ 16, R> 16 mg/L
S. saprophyticus (uncomplicated UTI only)	S≤ 64, R> 64 mg/L
E. faecalis (uncomplicated UTI only)	S ≤ 64, R> 64 mg/L
S. agalactiae (group B streptococci) (uncomplicated UTI only)	S ≤ 64, R> 64 mg/L
E. coli (uncomplicated UTI only)	S ≤ 64, R> 64 mg/L

For more information on Minimum inhibitory concentration (MIC) breakpoints, please refer to https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

The following table contains an overview of relevant micro-organisms for the indication. Commonly sensitive species:
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus saprophyticus
Enterococcus faecalis
Escherichia coli

Types where acquired resistance can be a problem:
Citrobacter species
Enterobacter species
Klebsiella species

Inherently resistant organisms:
Proteus species
Pseudomonas species
Serratia species

5.2 Pharmacokinetic properties

Absorption
Each capsule contains macrocrystalline nitrofurantoin, that dissolves and absorbs slower than the nitrofurantoin microcrystals. Nitrofurantoin is rapidly absorbed in the upper part of the small intestine. Ingestion with food or milk promotes absorption. Plasma concentrations are low at therapeutic doses, with peaks usually lower than 1 µg/ml.

Distribution
60 to 77% of nitrofurantoin is loosely bound to plasma albumin. Distribution takes place between intra- and extracellular tissue components. Minor amounts of nitrofurantoin pass through the placenta.

Biotransformation
Approximately 60% of an administered dose of nitrofurantoin is primarily metabolised enzymatically to microbiologically inactive aminofurans, which can discolour the urine.

Elimination
The half-life in blood or plasma is estimated at about 60 minutes. In patients with normal kidney function and average dose, average values are 50 to 200 micrograms/ml nitrofurantoin in the urine.

5.3 Preclinical safety data

Animal studies have shown that administration of nitrofurantoin leads to degenerative changes in the ovaries and testes of rodents, at doses below those commonly used in clinical settings (converted into units of body surface area).
Treatment with nitrofurantoin during pregnancy in rodents showed embryotoxicity, including a decrease in growth and decrease in viability.
In the rat embryofetal development study, an increased number of resorptions, decreased body weights of live pups at birth and at day 4 postnatally, and decreased viability of pups at day 4 after birth were found in the 20 mg/kg b.w. per day dose group leading to a NOAEL of 10 mg/kg/day for embryotoxic effects.
Nitrofurantoin caused a clear toxic effect on spermatogenesis in rats at a dose of 10 mg/kg b.w. per day and higher. Ovarian degeneration/ atrophy occurred at higher doses.
Nitrofurantoin is mutagenic both in vitro and in vivo.
The long-term carcinogenicity studies showed the occurrence of tumours in female mice (ovaries) and a weak effect in male rats (bone and kidney).
Even though there is no clinical relevance of these findings, nitrofurantoin should only be used for long-term treatment if no therapeutic alternatives are available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Lactose monohydrate
Talc (E553b)

<u>50 mg hard capsules</u>
<u>Body</u>
Titanium dioxide (E171)
Gelatin
<u>Cap</u>
Yellow iron oxide (E172)
Titanium dioxide (E171)
Gelatin

<u>100 mg hard capsules</u>
<u>Body and Cap</u>
Titanium dioxide (E171)
Yellow iron oxide (E172)
Gelatin

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/Aluminium foil blister pack containing 20 or 30 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Kora Corporation Ltd t/a Kora Healthcare
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8 MARKETING AUTHORISATION NUMBER

PA1748/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th July 2024

10 DATE OF REVISION OF THE TEXT