SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

NITROFURANTOIN RAZ 100 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg of nitrofurantoin in macrocrystals form.

Excipient with known effect:

Each 100 mg capsule contains 180.80 mg of Lactose monohydrate. (see section 4.4)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard, gelatin capsules.

Size '2' opaque yellow cap and opaque yellow body hard gelatin capsules, imprinted with “EM29” with 360 deg. thin band, in black ink on cap, filled with yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nitrofurantoin Raz 100 mg is indicated for the treatment of and prophylaxis against acute or recurrent, uncomplicated lower urinary tract infections when due to susceptible microorganisms in adults and adolescents 12 years and older.

4.2 Posology and method of administration

Posology

Adults and adolescents 12 years and older:

For the treatment of infections:

100 mg, 3-4 times a day.

Treatment should be continued, as a rule, for 1 week, or at least 3 days after obtaining sterile urine.

Administration in prophylaxis and suppression -

When treatment is justified, a daily dose of 100 mg at bedtime is suggested for adults and adolescents 12 years and older.

This medicine is not suitable for use in children under 12 years of age.

Children and Adolescents

Nitrofurantoin Raz 100mg is intended for children 12 years and older.

Do not use NITROFURANTOIN RAZ 100 mg in infants under three months of age.

Infants 3 months to children 12 years of age:

Nitrofurantoin Raz 100mg is not indicated for infants between 3 months to children 12 years of age as the Capsules cannot be crushed or chewed, and the content of the capsule should not be opened or dispersed to adjust the dose per weight in this age group.

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.

Swallow the capsules whole. (the Capsules should not be splited, crushed or chewed)

In the absence of stability and pharmacokinetic data, the capsule should not be

opened and dispersed.

This medicine should always be taken with food or milk. Taking Nitrofurantoin capsules with a meal improves absorption and is important for optimal efficacy.

4.3 Contraindications

- Hypersensitivity to nitrofurantoin, other nitrofurans or to any of the excipients listed in section 6.1.
- Patients suffering from renal dysfunction with an eGFR below 45 ml/minute.
- 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 precautions for use

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.

Pulmonary adverse reactions

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

discontinued immediately. **Signs of pulmonary damage include difficulty and or pain when breathing, shortness of breath and coughing up blood or mucus.**

Chronic pulmonary reactions

Chronic pulmonary reactions (including pulmonary fibrosis and diffuse interstitial pneumonitis) can develop insidiously and can often occur in elderly patients. Close monitoring of the lung disease of patients receiving long-term therapy is indicated (especially in the elderly).

Acute pulmonary reactions

Pulmonary reactions may be acute and usually occur within the first week of treatment. Increased vigilance for respiratory symptoms in patients who have just started therapy is warranted (especially in the elderly).

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

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.

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 (paraesthesiae).

Nitrofurantoin should be used with caution in 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 conditions of patients receiving long-term therapy is warranted (especially in the elderly).

Patients 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.

For long-term treatment, monitor patients closely for evidence of hepatitis or pulmonary symptoms or other evidence of toxicity.

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

Important information about some of the ingredients:

Nitrofurantoin Raz 100 mg contains Lactose monohydrate.

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

1. Increased absorption with food or agents delaying gastric emptying.

2. Decreased absorption with magnesium trisilicate.

3. Decreased renal excretion of nitrofurantoin by probenecid and sulphinpyrazone.

4. Decreased anti-bacterial activity by carbonic anhydrase inhibitors and urine alkalisation.

5. Anti-bacterial antagonism by quinolone anti-infectives.

6. Interference with some tests for glucose in urine.

7. As nitrofurantoin belongs to the group of Antibacterials, it will have the following interactions:

• Oestrogens: In common with other antibiotics, nitrofurantoin may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of oestrogen-containing contraceptive products. Therefore, patients should be warned appropriately and extra contraceptive precautions taken.

• Typhoid Vaccine (oral): Antibacterials inactivate the 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 the 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.

Fertility

No data available.

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

A tabulated list of undesirable effects (derived from clinical studies and post-marketing surveillance with nitrofurantoin) is outlined below.

The undesirable effects are listed according to organ systems and following frequencies:
Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10,000 to <1/1000), Very rare (<1/10,000), Not known (cannot be estimated from the available data).

System organ class **MedDRA**	*Very common (≥1/10)*	*Common (≥1/100 to <1/10)*	*Uncommon (≥1/1000 to <1/100)*	*Rare (≥1/10,000 to <1/1000)*	*Very rare (<1/10,000)*	*Not known (cannot be estimated from the available data)*
Blood and lymphatic system disorders				Aplastic anaemia		Agranulocytosis, leucopenia, granulocytopenia, haemolytic anaemia, thrombocytopenia, glucose-6-phosphate-de - hydrogenase deficiency anaemia, megaloblastic anaemia and eosinophilia
Cardiac disorders				Collapse and cyanosis		
Congenital, familial and genetic Disorders						Acute porphyria
Immune system disorders						Allergic skin reactions, angioneurotic oedema and anaphylaxis
Infections and infestations						Superinfections by fungi or resistant organisms such as Pseudomonas. However, these are limited to the genitourinary tract
Psychiatric disorders						Psychotic reactions, depression, euphoria, confusion

System organ class **MedDRA**	*Very common (≥1/10)*	*Common (≥1/100 to <1/10)*	*Uncommon (≥1/1000 to <1/100)*	*Rare (≥1/10,000 to <1/1000)*	*Very rare (<1/10,000)*	*Not known (cannot be estimated from the available data)*
Nervous system disorders						Benign intracranial hypertension, peripheral neuropathy including optic neuritis (sensory as well as motor involvement), nystagmus, vertigo, dizziness, headache and drowsiness
Respiratory, thoracic and mediastinal disorders						Pulmonary fibrosis; possible association with lupus-erythematous-like syndrome, acute pulmonary reactions, * subacute pulmonary reactions, * chronic pulmonary reactions, *cough, dyspnoea
Gastrointestinal disorders						Sialadenitis, pancreatitis, anorexia, emesis, abdominal pain, diarrhoea and nausea
Hepatobiliary disorders						Chronic active hepatitis (fatalities have been reported), hepatic necrosis, autoimmune hepatitis, cholestatic jaundice
Skin and subcutaneous tissue disorders						Drug Rash with Eosinophilia And Systemic Symptoms (DRESS syndrome), lupus-like syndrome associated with

System organ class **MedDRA**	*Very common (≥1/10)*	*Common (≥1/100 to <1/10)*	*Uncommon (≥1/1000 to <1/100)*	*Rare (≥1/10,000 to <1/1000)*	*Very rare (<1/10,000)*	*Not known (cannot be estimated from the available data)*
						pulmonary reaction, exfoliative dermatitis and erythema multiforme (including Stevens-Johnson Syndrome), maculopapular, erythematous or eczematous eruptions, cutaneous vasculitis, urticaria, rash, and pruritus, transient alopecia
Renal and urinary disorders						Yellow or brown discolouration of urine, interstitial nephritis
General disorders and administration site conditions						Asthenia, fever, chills, drug fever and arthralgia
Investigations						False positive urinary glucose

*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.

Treatment should be stopped at the first sign of hepatotoxicity.
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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health

according to the National Regulation by using an online form: https://sideeffects.health.gov.il.

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. 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 the drug.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use – nitrofuran 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

The nitrofurantoin macrocrystals are specially formulated. The controlled crystal size of the active substance nitrofurantoin macrocrystals, alters the speed of absorption to reduce the incidence of nausea without any decrease in antibacterial efficacy. Clinical and animal studies indicate that nitrofurantoin macrocrystals therapy decreases the likelihood of nausea in patients who might experience these symptoms on nitrofurantoin therapy. This special formulation of nitrofurantoin had not caused any decrease in antibacterial efficacy.

Absorption

Orally administered nitrofurantoin is readily absorbed in the upper gastrointestinal tract at a slower rate and to a reduced extent when compared to microcrystalline nitrofurantoin. Blood concentrations at therapeutic dosage are usually low.

Elimination

Maximum urinary excretion usually occurs 4-5 hours after administration of macrocrystalline nitrofurantoin. Urinary drug dose recoveries of approximately 25-30% are obtained. It has an elimination half-life of about 30 minutes or less.

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 observations.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Lactose Monohydrate
Pregelatinized starch
Talc

Capsule shell and body: (EHGC '2' yellow OP/ yellow OP)
Purified water
Titanium dioxide (E171)
Quinoline yellow (E104)
Iron oxide yellow (E172)
Gelatin

Printing black ink TEK SW 9008:
Shellac
Propylene glycol
Potassium hydroxide
Black iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions, but it is recommended to be stored in room temperature.

6.5 Nature and contents of container

Nitrofurantoin Raz 100 mg Capsules are supplied in PVC white opaque/aluminium foil blisters (Each blister contains 10 capsules).

Nitrofurantoin Raz 100 mg Capsules are available in packs of 20 and 30 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER and importer

RAZ PHARMACEUTICS LTD.

31 Gesher Haetz, Industrial Park, Emek Hefer, Israel

8 MARKETING AUTHORISATION NUMBER(S)

175-65-37315-99

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