Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nitrofurantoin 50 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 50 mg nitrofurantoin.
Excipient with known effect
Each hard capsule contains 98.33 mg lactose (as monohydrate).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule.
Hard capsule (15.5 mm in length) with a yellow cap and ivory-yellow body, containing yellow or yellow-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nitrofurantoin is indicated for the treatment of and prophylaxis against acute or recurrent, uncomplicated lower urinary tract infections either spontaneous or following surgical procedures caused by micro-organisms sensitive to nitrofurantoin (see Section 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Adults
Acute uncomplicated lower urinary tract infections (UTIs): 50 mg four times daily for seven days.

Severe chronic recurrence (UTIs): 100 mg four times daily for seven days. In the event of severe nausea, the dose may be reduced, but not below the adult equivalent of 200mg/day. Should nausea persist the drug should be withdrawn.

Long term prophylaxis: 50-100 mg once a day at bedtime. See precautions and warnings (section 4.4) for risks associated with long-term therapy.

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

Paediatric population
Children over the age of 10 years:
As per adult posology.

Children and Infants over three months of age:
Acute urinary tract infections: 3mg/kg day in four divided doses for seven days.
Prophylaxis: 1mg/kg, once a day.

Consideration must be given to national guidance on paediatric prescribing of nitrofurantoin.
The use of this medicine in the form of hard capsule may not be suitable for administration to younger children. Other pharmaceutical forms may be more appropriate for administration to this population.

Elderly
As per adult posology. Dosage adjustments may be necessary for elderly patients with renal impairment (see section 4.3, 4.4 and 4.8). See precaution and risks to elderly patients associated with long-term therapy (see section 4.4 and 4.8).

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

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 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 the active substance or 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.
- G6PD deficiency: May produce neonatal haemolysis if used at term. Only small amounts are present in breast milk but could be enough to produce haemolysis in G6PD deficient infants (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.
- In patients who have previously had a lung or liver reaction or a peripheral neuropathy after use of nitrofurantoin or other nitrofurans

4.4 Special warnings and precautions for use

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.

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

Neuropathy
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).

Patients with Renal impairment
Nitrofurantion should be used with caution in patients with renal impairment see sections 4.2 and 4.3. Patients with mild to moderate renal dysfunction will require adequate monitoring, as they may experience an increase in pulmonary adverse events when taking Nitrofurantoin (see Section 4.2 and 4.8).

Nitrofurantoin is contra-indicated in patients with severe renal impairment with an eGFR below 45 mL/min (see section 4.3).

Pulmonary reactions
Acute, subacute and chronic pulmonary reactions have been observed in patients treated with nitrofurantoin. If these reactions occur, nitrofurantoin should be discontinued immediately. Acute pulmonary reactions occur within the first week of treatment and are reversible. If any of the following respiratory reactions occur the drug should be discontinued. 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.
Chronic pulmonary reactions (including pulmonary fibrosis and diffuse interstitial pneumonitis) can develop insidiously. Close monitoring of the pulmonary conditions of patients receiving long-term therapy is warranted (especially in the elderly).

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. Lupus-like syndrome associated with pulmonary reactions to nitrofurantoin has been reported (see section 4.8).

Hematologic Effects
Nitrofurantoin may cause haemolysis in patients with glucose-6-phosphate Dehydrogenase deficiency (Ten percent of black patients and a variable Percentage of ethnic groups of Mediterranean, Near Eastern and Asian origin). Haemolysis ceases when the drug is discontinued. Agranulocytosis, leucopenia, granulocytopenia, haemolytic anaemia, thrombocytopenia, glucose-6-phosphatedehydrogenase deficiency anaemia, megaloblasticanaemia and eosinophilia have occurred. Aplastic anaemia has been reported rarely. Cessation of therapy has generally returned the blood picture to normal.

Clostridium difficile associated diarrhea (CDAD)
Gastrointestinal reactions may be minimised by taking the drug with food or milk or by adjustment of dosage.
Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including nitrofurantoin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.

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. 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. If hepatitis occurs, the drug should be withdrawn immediately and appropriate measures should be taken. Rarely liver failure (which may be fatal) have been reported after nitrofurantoin usage.

Long-term prophylaxis
The benefit-risk for long-term prophylaxis is considered positive on the condition that the benefits outweigh the potential risk and if no suitable alternative is available. Continuous antimicrobial prophylaxis as prevention of recurrent urinary tract infections should only be considered after counselling and behavioural modification were tried, and when non-antimicrobial measures were unsuccessful.
For long term treatment, monitor patient closely for appearance of hepatitis (or liver damage), pulmonary or neurological symptoms and other evidence of toxicity. Discontinue treatment with nitrofurantoin if otherwise unexplained pulmonary, hepatotoxic, haematological or neurologic syndromes occur.

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

Laboratory Tests
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).

Excipients

- Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
- This medicine contains less than 1 mmol sodium (23mg) per dosage unit, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

- Concomitant administration of magnesium trisilicate reduces absorption of nitrofurantoin.
- Uricosuric drugs such as probenecid and sulphinpyrazone may inhibit renal tubular secretion of nitrofurantoin. The resulting increase in serum levels may increase toxicity. Decreased urinary levels could reduce efficacy as a urinary tract antibacterial.
- Concurrent use with quinolones is not recommended.

- There may be decreased antibacterial activity for nitrofurantoin in the presence of carbonic anhydrase inhibitors and urine alkalinising agents.
- As a result of the presence of nitrofurantoin when tested for reducing substances, a false positive reaction for glucose in the urine may occur. The presence of food or agents delaying gastric emptying can result in increased absorption of nitrofurantoin.
- As Nitrofurantoin belongs to the group of antibacterials it will have the following resulting interactions:

Typhoid Vaccine (oral): Antibacterials inactivate oral typhoid vaccine.

4.6 Fertility, pregnancy and lactation

Pregnancy
Nitrofurantoin is contraindicated in pregnant patients at term (during labour and delivery). As with all drugs, maternal side-effects, should they occur, may adversely affect the course of the pregnancy. The drug should be used at the lowest effective dose only after careful assessment of benefits against potential risks.
Based on animal reproduction studies and clinical experience in humans over many years, there is no evidence of any teratogenic effects of nitrofurantoin on the foetus.

Breast-feeding
Caution should be exercised while breast feeding an infant known or suspected to have any erythrocyte enzyme deficiency as nitrofurantoin is detected in trace amounts in breast milk.

Fertility
A transient arrest in spermatogenesis and decreased sperm counts were observed in men at supratherapeutic doses.
Clinical dosages have not been associated with male infertility.

4.7 Effects on ability to drive and use machines

Nitrofurantoin has major influence on the ability to drive and use machines. It may cause dizziness and drowsiness. Patients should be advised not to drive or operate machinery if affected in this way until such symptoms go away.

4.8 Undesirable effects

A tabulated list of undesirable effects is outlined below:
The undesirable effects are listed according to organ systems and following frequencies:

Rare (≥1/10 000 to <1/1 000)
Not known (cannot be estimated from the available data)

System organ class	Frequency	Adverse reaction
Infections and infestations	Not known	Superinfections by fungi or resistant organisms such as Pseudomonas. However, these are limited to the genitourinary tract
Blood and lymphatic system disorders	Rare Not known	Aplastic anaemia Agranulocytosis, leucopenia, granulocytopenia, haemolytic anaemia, thrombocytopenia,glucose¬6-phosphatedehydrogenase deficiency anaemia, megaloblastic anaemia and eosinophilia
Immune system disorders	Not known	Allergic skin reactions, angioneurotic oedema, anaphylaxis and cutaneous vasculitis
Psychiatric disorders	Not known	Depression, euphoria, confusion, psychotic reactions
Nervous system disorders	Not known	Peripheral neuropathy including optic neuritis (sensory as well as motor involvement), nystagmus, vertigo, dizziness, headache and drowsiness. Benign intracranial hypertension
Cardiac disorders	Rare	Collapse and cyanosis
Respiratory, thoracic and mediastinal disorders	Not known	Permanent impairment of pulmonary function, pulmonary fibrosis; possible association with lupus-erythematous-like syndrome.

		Acute pulmonary reactions* Subacute pulmonary reactions* Chronic pulmonary reactions** Bronchiolitis obliterans organising pneumonia Dyspnoea, cough
Gastrointestinal disorders	Not known	Sialadenitis, Pancreatitis, Nausea, Anorexia, Emesis, Abdominal pain and Diarrhoea.
Hepatobiliary disorders	Rare Not known	Liver failure (which may be fatal) Chronic active hepatitis (fatalities have been reported), Hepatic necrosis, autoimmune hepatitis, cholestatic jaundice.
Skin and subcutaneous tissue disorders	Not known	Transient alopecia Exfoliative dermatitis and erythema multiforme (including Stevens-Johnson Syndrome), maculopapular, erythematous or eczematous eruptions, urticaria, rash, and pruritus. Lupus-like syndrome associated with pulmonary reaction. Drug Rash With Eosinophilia And Systemic Symptoms (DRESS syndrome)
Renal and urinary disorders	Not known	Yellow or brown discolouration of urine, Interstitial nephritis
Congenital, familial and genetic disorders	Not known	Acute porphyria
General disorders and administration site conditions	Not known	Asthenia, fever, chills, drug fever and arthralgia
Investigations	Not known	False positive urinary glucose

*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.

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. 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 tract pathogens. The mechanism of action of nitrofurantoin is based on reduction to reactive intermediates. These inhibit enzymes involved in energy metabolism, such as in the Krebs cycle, interfering with the energy supply for normal growth and maintenance of bacteria. They also bind to bacterial ribosomal proteins at different sites, resulting in disruption of bacterial protein synthesis. Transferable resistance to nitrofurantoin is a rare phenomenon. There is no cross resistance to antibiotics and sulphonamides.

Nitrofurantoin is specifically indicated for the treatment of infections when due to susceptible strains of *Escherichia coli,* enterococci, staphylococci, *Citrobacter, Klebsiella* and *Enterobacter*.
Most strains of Proteus and Serratia are resistant. All Pseudomonas strains are resistant.

Susceptibility testing breakpoints
MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for nitrofurantoin and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx.

5.2 Pharmacokinetic properties

Absorption
Nitrofurantoin is readily absorbed in the upper gastrointestinal tract. Intake with food or milk increases absorption.

Distribution
Nitrofurantoin is highly soluble in urine but plasma concentrations are low with peak levels usually less than 1 mcg/ml.

Biotransformation
Nitrofurantoin is loosely bound to plasma albumin (60-70 %). The molecule is readily distributed into intra and extracellular compartments. However, substantial tissue concentrations are not expected since the drug is rapidly excreted and readily degraded by tissue enzymes. The drug crosses the placenta in small amounts.

Elimination
The elimination half life in blood or plasma after IV injection is about 20 minutes; and after oral administrations of macrocrystals, less than 60 minutes. Following a single dose of nitrofurantoin about 25% is found unchanged in the urine over 24 hours.

5.3 Preclinical safety data

The available genotoxicity data indicate that nitrofurantoin is a mutagen. Two-year carcinogenicity studies in rats and mice reported carcinogenic effects. The relevance of the genotoxic and carcinogenic potential of nitrofurantoin to human is unknown. Extensive clinical use of nitrofurantoin over 65 years has not found any conclusive evidence for carcinogenic effects at therapeutic dosages.
In rats, at high doses a temporary halt in spermatogenesis was observed in male and ovarian degeneration and atrophy occurred in female. No decreased fertility was observed in animal studies.
In rats, the administration of nitrofurantoin during gestation has been shown to be toxic to the embryo, including decreased growth.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Lactose monohydrate Maize starch
Talc

Capsule shell
Iron oxide yellow (E 172)
Titanium dioxide (E 171)
Gelatin

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

PVC/Alu blister containing 14, 15, 28, 30, 56, 60, 84 or 90 hard capsules.
For NL - PVC/Alu blister containing 14, 15, 20, 28, 30, 56, 60, 84 or 90 hard capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Activase Pharmaceuticals Limited
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Nicosia
1060
Cyprus

8 MARKETING AUTHORISATION NUMBER

PA1567/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 15th November 2024

10 DATE OF REVISION OF THE TEXT

December 2025