SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nitrofurantoin Adalvo 100 mg prolonged-release capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release hard capsule contains the equivalent of 100 mg nitrofurantoin in the form of nitrofurantoin macrocrystals and nitrofurantoin monohydrate.

Excipients with known effect:

Each capsule contains 74 mg lactose and 35 mg confectioner's sugar (containing 33 mg sucrose).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard prolonged-release capsule

Each capsule is approximately 19 mm long and 7 mm wide and has a blue opaque cap with imprinted "NTRF" in white ink and a yellow opaque body.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of and prophylaxis against acute or recurrent, uncomplicated lower urinary tract infections or pyelitis either spontaneous or following surgical procedures. It is indicated in adults, children and infants over 12 years of age.

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.

Nitrofurantoin is not indicated for the treatment of associated renal cortical or perinephric abscesses.

4.2 Posology and method of administration

Posology

Adults and children over 12 years of age.

The dose should be taken with food or milk (e.g., at mealtimes).

Acute or recurrent uncomplicated UTI and pyelitis -100mg twice daily for seven days.

Surgical Prophylaxis - 100 mg twice daily on the day of the procedure and 3 days thereafter.

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).

Children under *12 years*

This medicinal product is a fixed dosage and is therefore not suitable for children under 12 years.

Renal impairment

Nitrofurantoin is contraindicated in patients with renal dysfunction and in patients with an eGFR below of less than 45 ml/minute (see sections 4.3 & 4.4).

Method of administration

For oral use

4.3 Contraindications

Hypersensitivity to the active substance, 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

Nitrofurantoin is not effective for the treatment of parenchymal infections of a unilaterally 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 hepatic or pulmonary 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.

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 diseaseof 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).

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 signs of haemolysis in those with suspected glucose-6-phosphate dehydrogenase deficiency.

Gastrointestinal reactions may be minimised by taking the drug with food or milk, or by adjustment of dosage.

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.

For long term treatment monitor the patient closely for appearance of hepatic or pulmonary symptoms and other evidence of toxicity.

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

Excipients

Nitrofurantoin prolonged-release capsules contain lactose monohydrate and sucrose. Patients with rare hereditary problems of galactose intolerance, fructose intolerance, total lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

- Increased absorption with food or agents delaying gastric emptying.
- Decreased absorption with magnesium trisilicate.

- Decreased renal excretion of nitrofurantoin by probenecid and sulfinpyrazone.
- Decreased anti-bacterial activity by carbonic anhydrase inhibitors and urine alkalisation.
- Anti-bacterial antagonism by quinolone anti-infectives.
- Interference with some tests for glucose in urine.
- 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

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 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

This medicinal product may cause dizziness and drowsiness. In case any of this occurs, the patient should not drive or operate machinery until symptoms disappear.

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-phosphate dehydrogenase deficiency anaemia, megaloblastic anaemia and eosinophilia
Immune system disorders	Not known	Anaphylaxis, angioneuroticoedema , cutaneous vasculitis and allergic skin reactions
Psychiatric disorders	Not known	psychotic reactions, depression, euphoria, confusion
Nervous system disorders	Not known	Benign intracranial hypertension, peripheral neuropathy including optic neuritis (sensory as well as motor involvement), nystagmus, vertigo, dizziness, headache and drowsiness.
Cardiac disorders	Rare	Collapse and cyanosis
Respiratory, thoracic and mediastinal disorders	Not known	Pulmonary fibrosis; possible association with lupus-erythematous-like syndrome. acute pulmonary reactions * subacute pulmonary reactions, * chronic pulmonary reactions, * cough, dyspnoea,
Gastrointestinal disorders	Not known	Sialaodenitis, pancreatitis, anorexia, emesis, abdominal pain, diarrhea and nausea
Hepatobiliary disorders	Not known	Chronic active hepatitis**, hepatic necrosis, autoimmune hepatitis, cholestatic jaundice
Skin and	Not known	Lupus-like syndrome associated

subcutaneous tissue disorders		with pulmonary reaction. Drug Rash With Eosinophilia And Systemic Symptoms (DRESS syndrome), exfoliative dermatitis and erythema multiforme (including Stevens-Johnson Syndrome), maculopapular, erythematous or eczematous eruptions, urticaria, rash, and pruritis, Transient alopecia
Renal and urinary disorders	Not known	Interstitial nephritis, yellow or brown discolouration of urine,
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 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

**Can be fatal

Reporting of suspected side effects

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 Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

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

Management

There is no specific antidote, however, nitrofurantoin can be haemodialysed if necessary. Standard treatment consists in the induction of emesis or gastric lavage in cases of recent ingestion (within one hour). Monitoring of full blood count, hepatic

function and pulmonary function tests are recommended. A high fluid intake should be maintained to promote urinary excretion of nitrofurantoin.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Nitrofurantoin is a broad spectrum antibacterial agent, active against the majority of urinary pathogens. It is bactericidal in renal tissue and throughout the urinary tract. The wide range of organisms sensitive to the bacterial activity include *Escherichia coli, Enteroccus faecalis, Klebsiella species, Enterobacter species, Staphylococcus species: (eg S. aureus, S. saprophyticus, S. epidermidis)*

Clinically, most common urinary pathogens are sensitive to nitrofurantoin. Some strains of *Enterobacter* and *Klebsiella* are resistant. Nitrofurantoin is not active against most strains of *Proteus* species or *Serratia* species. It has no activity against *Pseudomonas* species.

5.2 Pharmacokinetic properties

Each Nitrofurantoin Adalvo 100 mg prolonged - release capsule contains two forms of nitrofurantoin. 25% of the dose is macrocrystalline nitrofurantoin which has slower dissolution and absorption than nitrofurantoin monohydrate. The remaining 75% of the dose is nitrofurantoin monohydrate contained in a powdered blend which on exposure to gastric and intestinal fluids forms a gel matrix resulting in a modified release of active ingredient over time. Combined these systems provide a clinically effective bactericidal urine concentration at therapeutic doses.

Distribution

Plasma nitrofurantoin concentrations at therapeutic doses of the Nitrofurantoin Adalvo 100mg prolonged-release capsule are low, with peak levels usually less than 1 mcg/ml. Nitrofurantoin is highly soluble in urine to which it may impart a brown colour. Unlike many drugs the presence of food or agents delaying gastric emptying increases the bioavailability of the Nitrofurantoin Adalvo 100mg prolonged-release capsules.

Elimination

Approx. 20-25% of the total single dose of nitrofurantoin is recovered from the urine unchanged over 24 hours.

5.3 Preclinical safety data

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Talc
Maize starch
Carbomer
Povidone
Lactose monohydrate
Sucrose
Magnesium stearate

Capsule shell:
Iron oxide yellow
Iron oxide black
Titanium dioxide (E 171)
Gelatin
Indigo Carmine (E 132)

Printing ink
Shellac
Propylene glycol (E 1520)
Strong ammonia solution
Water, purifed
Potassium hydroxide
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25° C.

6.5 Nature and contents of container

Carton box containing PVC-Aclar/Aluminium blisters.

Pack sizes of 2 capsules, 14 capsules or 20 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

Adalvo Limited

Malta Life Science Park,

Level 1, Building 4,

Sir Temi Zammit Buildings,

San Gwann, SGN 3000, Malta

8 MARKETING AUTHORISATION NUMBER(S)

PL 51289/0019

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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