AUSTRALIAN PRODUCTINFORMATION – FUDANTIN (NITROFURANTOIN MACROCYSTAL)

1. NAME OF THE MEDICINE

Nitrofurantoin Macrocrystal

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FUDANTIN capsules contain either 50 mg or 100 mg of nitrofurantoin as the active.

Excipient with known effect:

Lactose monohydrate – Contains sugars as lactose

For the full list of excipients, see Section 6.1 List of excipients.

Note:

FUDANTIN (nitrofurantoin macrocrystals) is a larger crystal form of nitrofurantoin. The absorption of FUDANTIN is slower and the excretion of FUDANTIN is somewhat less, when the two are compared. The reduced incidence of gastrointestinal intolerance with FUDANTIN is probably due to delayed and decreased absorption; this however does not significantly reduce clinical effectiveness.

3. PHARMACEUTICAL FORM

50 mg capsules: Hard gelatin capsule size '3' with "A9" imprint on opaque yellow cap and plain opaque white body containing pale yellow granular powder.

100 mg capsules: Hard gelatin capsule size '2' with "A8" imprint on opaque yellow cap and plain opaque yellow body containing pale yellow granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of urinary tract infections such as cystitis and pyelitis when due to susceptible pathogens. Nitrofurantoin does not reach effective levels in plasma and consequently is not indicated for cortical or perinephric abscesses and in cases of prostatitis.

4.2 Dose and method of administration

To be taken with food or milk.

Adults: 50-100 mg four times a day. DO NOT EXCEED 400 mg DAILY.

Prophylactic therapy: 50 mg or 100 mg nocte.

Children: Should be calculated on the basis of 5-7 mg/kg body weight per 24 hours to be given in divided doses four times a day.

Nitrofurantoin should not be administered to infants under one month of age.

Therapy should be continued for at least one week and for at least 3 days after sterility of the urine is obtained. Continued infection indicates the need for re-evaluation. If the drug is to be used for prophylactic or for long-term suppressive therapy, consideration should be given to finding the lowest effective dose.

4.3 Contraindications

Anuria and oliguria or extensive impairment of renal function (creatinine clearance under 60 mL/min or clinically significant elevated serum creatinine); hypersensitivity to furan derivatives; nitrofurantoin should not be administered to pregnant women during labour and delivery, or when the onset of labour is imminent or to infants under one month of age because of the possibility of producing a haemolytic anaemia due to immature enzyme systems (glutathione instability) in the early neonatal period.

4.4 Special warnings and precautions for use

Peripheral Neuropathy

Peripheral neuropathy (including optic neuritis), which may become severe or irreversible, has occurred. Fatalities have been reported. Conditions such as renal impairment (creatinine clearance under 60 mL/min or clinically significant elevated serum creatinine), anaemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency, and debilitating disease may enhance the occurrence of peripheral neuropathy. Patients receiving long-term therapy should be monitored periodically for changes in renal function. If numbness or tingling occurs in any area, administration of the drug should be discontinued (see Section 4.8 Adverse effects (undesirable effects) - Neurological).

Hepatic Reactions

Hepatic reactions, including 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 liver function. If hepatitis occurs, the drug should be withdrawn immediately and appropriate measures should be taken (see Section 4.8 Adverse effects (undesirable effects) - Hepatic).

Pulmonary Reactions

Acute, subacute or chronic pulmonary reactions have been observed in patients treated with nitrofurantoin. These reactions can be life threatening; therefore if they occur treatment should be stopped immediately. Chronic pulmonary reactions (diffuse interstitial pneumonitis or pulmonary fibrosis, or both) can develop insidiously. These reactions occur rarely and generally in patients receiving therapy for six months or longer. Close monitoring of the pulmonary condition of patients receiving long-term therapy is warranted and requires that the benefits of therapy be weighed against potential risks (see Section 4.8 Adverse effects (undesirable effects) - Pulmonary hypersensitivity).

Haemolytic Anaemia

Haemolytic anaemia of the primaquine-sensitivity type has been induced by nitrofurantoin. The haemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the affected patients' red blood cells. This deficiency is found in 10% of African descent individuals and in a small percentage of ethnic groups of Mediterranean and Near Eastern origin. G6PD deficiency has also been reported occasionally amongst Caucasian groups. Any sign of haemolysis is an indication to discontinue the drug. Haemolysis ceases when the drug is withdrawn.

Colitis

Antibiotic associated Pseudomembranous colitis has been reported with many antibacterials including sporadic reports with nitrofurantoin. A toxin produced with *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine may prolong and/or worsen the condition and should not be used. Patients should be advised that nitrofurantoin may cause brownish discolouration of the urine.

Use in hepatic impairment

If hepatitis occurs, the drug should be withdrawn immediately and appropriate measures should be taken (see Section 4.8 Adverse effects (undesirable effects) - Hepatic).

Use in renal impairment or acidosis

In the presence of impairment of renal function or acidosis, administer FUDANTIN with caution. If employed under such circumstances the blood pH, CO_2-content or combining power and urea nitrogen or non-protein nitrogen should be followed closely. This is particularly important if treatment is continued beyond fourteen days.

Use in the elderly

No data available.

Paediatric use

Nitrofurantoin should not be administered to infants under one month of age. For information regarding dosage in children see Section 4.2 Dose and method of administration.

Effects on laboratory tests

Nitrofurantoin can interfere with certain laboratory tests e.g. serum bilirubin (false positive or spuriously high reading), urine creatinine (false positive, or accurate readings cannot be made, due to interference), serum urea (no accurate reading due to interference), urine glucose (false positive or spuriously high readings). Urine glucose tests dependent on glucose oxidase are not affected e.g. Clinistix and Testape.

4.5 Interactions with other medicines and other forms of interactions

The excretion of nitrofurantoin is decreased by acidifying drugs, whereby potentiation of nitrofurantoin may occur. Conversely, alkalinising drugs increase the rate of excretion and may diminish the effect of nitrofurantoin. Phenobarbitone has an inhibitory action on nitrofurantoin. Uricosuric drugs, such as probenecid and sulfinpyrazone, can inhibit renal tubular secretion of nitrofurantoin. The resulting increase in nitrofurantoin serum levels may increase toxicity and the decreased urinary levels could lessen its efficacy as a urinary tract antibacterial.

Antacids reduce the potency of the drug. Patients should be advised not to use antacid preparations at the same time as nitrofurantoin.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Rats given large doses of nitrofurantoin have developed lesions in seminiferous tubules which vary from atrophy to arrest of spermatogenesis. The arrest of spermatogenesis was reversible and treated male rats sired normal litters after recovery.

In man, nitrofurantoin can decrease sperm counts and produce abnormal testicular histology suggestive of arrested spermatogenesis.

Use in pregnancy – Pregnancy Category A – short term therapy

Nitrofurantoin has had widespread clinical use for many years. Studies, to date, have not shown a potential for nitrofurantoin to cause birth defects.

Nitrofurantoin crosses the placenta, and caution should be exercised when administering nitrofurantoin at term or to infants under one month of age because of the possibility of producing a haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to immature enzyme systems in the early neonatal period.

Use in lactation

Although studies have shown that the amount of nitrofurantoin excreted in breast milk after normal therapeutic doses is negligible, the possibility of producing a haemolytic anaemia due to immature enzyme systems in the early neonatal period should be considered when administering the drug to nursing mothers.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

Gastrointestinal

Nausea with associated anorexia and emesis is the most common adverse effect of nitrofurantoin therapy. This can be reduced by taking the drug with food or milk. Less frequent are abdominal pain and diarrhoea and, rarely, hepatitis - these latter dose-related toxic effects can be minimised by reduction of the dose especially in females on long term treatment. Dyspepsia, flatulence and constipation have also been reported.

Neurological

Polyneuropathy, (including optic neuritis) which starts peripherally with initial sensory loss and paraesthesia but progresses to motor loss often with severe muscle atrophy, has occurred during nitrofurantoin therapy. A predisposing condition in most of these patients was renal failure which often was accompanied by anaemia, diabetes, electrolyte imbalance, vitamin B deficiency and debilitating disease. After stopping nitrofurantoin therapy, further deterioration is generally halted and total or partial regression occurs in almost 80% of those affected. These reactions may be severe or irreversible, but are rarely fatal. Polyneuropathy occurs in adults and children.

If numbness or tingling occurs in any area, administration of the drug should be discontinued. Headache, dizziness, nystagmus, drowsiness, asthenia, vertigo, amblyopia, depression, euphoria, confusion, psychotic reactions and benign intracranial hypertension have also been reported.

Hepatic

Hepatic reactions can occur, including hepatitis, cholestatic jaundice, chronic active hepatitis and hepatic necrosis. These reactions can be life threatening, therefore if they occur treatment should be stopped immediately. Chronic hepatic reactions can develop insidiously, but usually occur in patients on therapy for 5 months or longer. Patients on prolonged therapy should be re-examined at intervals not exceeding 6 months.

Hypersensitivity reactions of several types have been reported:

a) Pulmonary hypersensitivity - can be acute, sub-acute or chronic. These reactions can be life threatening; therefore if they occur treatment should be stopped immediately.

   Acute reactions are commonly manifested by fever, chills, cough, chest pain, dyspnoea and pulmonary infiltration with consolidation and pleural effusion on X-ray and eosinophilia. The acute reaction usually occurs in the first week of therapy and resolves on withdrawal of the drug.

   Sub-acute or chronic pulmonary reactions are associated with prolonged therapy. Insidious onset of malaise, dyspnoea on exertion, cough, cyanosis, altered pulmonary function and roentgenographic and histological findings of diffuse interstitial

pneumonitis and fibrosis are common manifestations. Patients on prolonged therapy should be re-examined at intervals not exceeding 6 months.

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. Pulmonary function may be impaired permanently, even after cessation of therapy. The risk is greater when chronic pulmonary reactions are not recognised early.

Changes in ECG may occur associated with pulmonary reactions. Cardiopulmonary failure leading to collapse and death has been reported.

b) Dermatological reactions - exfoliative dermatitis, erythema multiforme, (including Stevens-Johnson syndrome) maculopapular, erythematous or eczematous eruptions and transient alopecia may occur.

c) Other sensitivity reactions have included Lupus like syndrome and anaphylaxis, asthma attacks in patients with a history of asthma, urticaria, rash, pruritis, drug fever, angioedema, drug allergy, sialadenitis, pancreatitis and arthralgia.

Haematological Reactions

Haemolytic anaemia, leucopenia, granulocytopenia, eosinophilia, thrombocytopenia, agranulocytosis, aplastic anaemia and megaloblastic anaemia. Return of the blood picture to normal has followed cessation of therapy.

Miscellaneous Reactions

As with other microbial agents, urinary tract superinfections by resistant organisms (e.g. *Pseudomonas* or *Candida*) can occur. There are sporadic reports of *Clostridium difficile* superinfections, or pseudomembranous colitis, with the use of nitrofurantoin.

The most frequent laboratory test abnormalities reported with use of nitrofurantoin are as follows: eosinophilia, increased AST (SGOT), increased ALT (SGPT), decreased haemoglobin, increased serum phosphate.

The following laboratory adverse events also have been reported with the use of nitrofurantoin: glucose-6-phosphate dehydrogenase deficiency anaemia (see Section 4.4 Special warnings and precautions for use), agranulocytosis, leukopenia, granulocytopenia, haemolytic anaemia, thrombocytopenia, megaloblastic anaemia. In most cases, these hematologic abnormalities resolved following cessation of therapy. Aplastic anaemia has been reported rarely

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reportingproblems.

4.9 Overdose

There are very little data available on toxicity of nitrofurantoin after overdose. No toxic serum levels have been established.

Symptoms

Symptoms expected would be mainly extensions of side effects. Occasional incidents of acute overdosage have not resulted in any specific symptoms other than vomiting.

Treatment

There is no specific treatment of overdosage and no antidotes are recommended. Treatment is essentially symptomatic and supportive.

As nitrofurantoin is excreted rapidly in the urine administration of adequate amounts of fluid will hasten excretion of the absorbed drug. In a patient with normal renal function 50 to 250 mg/L are considered normal urine levels after taking a therapeutic dose.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Microbiology

FUDANTIN is bacteriostatic at low concentrations (1:100,000 to 1:200,000) and *in vitro* is considered to be bactericidal in higher concentrations. Its presumed mode of action is based upon its interference with several bacterial enzyme systems.

Nitrofurantoin is active against Gram-positive and Gram-negative urinary tract pathogens, particularly *Ecoli*, but *Ps aeruginosa* and some *Klebsiella*, *Aerobacter* and *Proteus* strains are insensitive.

Antibacterial Activity of Nitrofurantoin
(Garrod Lambert & O'Grady. "Antibiotic & Chemotherapy" p 43)

Organism	MIC (Minimum Inhibitory Concentration) nitrofurantoin microgram/mL
Staph aureus	4 - 30
Str pyogenes	10
Str viridans	8
Str faecalis	4 - 125
N gonorrhoeae	15
Esch coli	0.4 - >250
Proteus spp	7.5 - >200

Klebsiella-Aerobacter spp	25 - >200
Salmonella spp	5-15
Shigella spp	5
Ps aeruginosa	> 200

Urine levels reached with normal therapeutic doses are usually in the range of 1546 microgram/mL and levels above the MIC for the most sensitive organisms are detectable for about 6 hours.

Bacteria develop only a limited resistance to furan derivatives.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Nitrofurantoin is well absorbed orally and is rapidly excreted in the urine. The peak plasma level appears 1-2 hours after an oral dose and has been found not to exceed 2.5microgram/mL. 25-60% of nitrofurantoin is bound to serum proteins. The plasma half-life of the drug is 20 min. The average urinary drug recoveries following a therapeutic dose regimen (100 mg four times daily for 7 days) were reported to be 37.9% (day 1) and 35% (day 7) for the macrocrystalline dosage form.

Nitrofurantoin is excreted mainly in the unchanged form, the only metabolic pathway of importance involving reduction of the nitro group. Excretion is *via* the kidney both in the glomerular filtrate and by tubular secretion.

5.3 Preclinical safety data

Genotoxicity

Nitrofurantoin is mutagenic in certain bacterial systems and although it is not known how far this relates to the clinical situation the possibility of a permanent mutagenic effect on spermatozoa-producing cells requires that careful consideration be given to its use in young males.

It may be concluded that although nitrofurantoin has genotoxic properties *in vitro*, it is of low genotoxic potential in whole animals. Thus it is unlikely that the increased tumour incidences seen in male rats are due to genotoxic action.

Carcinogenicity

Nitrofurantoin has caused increases in the incidence of renal tubular cell adenomas when administered to male rats at 65-125 mg/kg/day for 2 years. The biological significance of this remains to be established. When administered to female mice at 375 mg/kg/day for 2 years, nitrofurantoin induced an increase in the incidence of benign ovarian tumours. It would appear that this effect may be secondary to its primary toxic activity of inducing ovarian atrophy and sterility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch

Purified talc

Lactose monohydrate

Gelatin

Water

Titanium dioxide

Iron oxide yellow

Sodium lauryl sulfate

Tekprint SW-9008 Black Ink

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

50 mg capsules: AI /PVC blister Pack containing 30 capsules.

100 mg capsules: AI /PVC blister Pack containing 30 capsules.

6.6 Special precautions for disposal

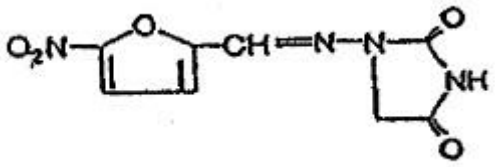
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Nitrofurantoin, 1-(5-nitrofurfurylideneamino) hydantoin, is a synthetic antibacterial nitrofuran derivative. It occurs as lemon yellow crystals, or fine powder, and is very slightly soluble in water or alcohol. However, solubility of the drug in water and urine increases with rises in pH. The sodium salt occurs as an orange coloured powder and is soluble in water. Nitrofurantoin darkens on exposure to light or to alkali and is decomposed upon contact with metals other than stainless steel or aluminium. Drug product should be protected from light and contact with metal other than stainless steel and aluminium blister Pack.

Chemical structure

Nitrofurantoin has the following chemical structure:



Nitrofurantoin has the following molecular formula and molecular weight : $C_8H_6N_4O_5$, 238.2.

CAS number

67-20-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

09 April 2026

10. DATE OF REVISION

N/A

Summary Table of Changes

Section changed	Summary of new information
All	New PI