

NEW ZEALAND DATA SHEET

1. NIFURAN TABLETS 50 MG AND 100 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg or 100 mg nitrofurantoin.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Yellow scored tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nitrofurantoin is an antibacterial agent specific for urinary tract infections.

Nitrofurantoin is indicated for the prophylaxis and treatment of infections of the genito-urinary tract due to susceptible bacteria.

Therapy with nitrofurantoin may be initiated before results of culture and susceptibility tests are known; therapy should be continued or altered, as appropriate, in accordance with results of the tests.

4.2 Dose and method of administration

Nitrofurantoin should be taken with food or milk.

Acute, Uncomplicated Urinary Tract Infections (acute cystitis)

Adults: Usual dose 50-100 mg four times daily for 7 days.

Children under 12 years: 5-7 mg/kg body weight per 24 hours, given in four divided doses (NB contraindicated in neonates under one month of age).

Prophylactic Therapy

Adults: Usual dose 50-100 mg at bedtime.

Children under 12 years: 1 mg/kg body weight per 24 hours, given in a single dose or in two divided doses (NB contraindicated in neonates under one month of age).

See section 4.4 Special warnings and precautions for use regarding risks associated with long-term therapy. Note: duration of long-term prophylaxis is up to 6 months. Long-term therapy should be continued beyond 6 months only when the benefits clearly outweigh the risks.

Paediatric population

See dosage information above.

4.3 Contraindications

Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine) are contraindications. Treatment of this type of patient carries an increased risk of toxicity because of impaired excretion of the medicine.

Because of the possibility of haemolytic anaemia due to immature erythrocyte enzyme systems (glutathione instability), the medicine is contraindicated in pregnant women during labour and delivery, or when the onset of labour is imminent. For the same reason, the medicine is contraindicated in neonates less than one month of age.

Nitrofurantoin is also contraindicated in those patients with known hypersensitivity to the medicine.

4.4 Special warnings and precautions for use

Warnings

Acute, subacute, or chronic pulmonary reactions have been observed in patients treated with nitrofurantoin. If these reactions occur, the medicine should be discontinued and appropriate measures taken. Reports have cited pulmonary reactions as a contributing cause of death.

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 Undesirable effects – Respiratory.)

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 medicine should be withdrawn immediately and appropriate measures should be taken.

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 per minute or clinically significant elevated serum creatinine), anemia, 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.

Cases of haemolytic anemia of the primaquine-sensitivity type have been induced by nitrofurantoin. Haemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. Haemolysis is an indication for discontinuing nitrofurantoin; haemolysis ceases when the medicine is withdrawn.

Precautions

Patients should be advised to take nitrofurantoin with food to further enhance tolerance and improve its absorption. Patients should be instructed to complete the full course of therapy; however, they should be advised to contact their physician if any unusual symptoms occur during therapy.

Patients should be advised not to use antacid preparations containing magnesium trisilicate at the same time as nitrofurantoin because of the possibility of impaired absorption.

The tendency of nitrofurantoin to impart a brown colour to the urine is of no clinical significance.

4.5 Interaction with other medicines and other forms of interaction

Antacids containing magnesium trisilicate, when administered concomitantly with nitrofurantoin, reduce both the rate and extent of absorption. The mechanism for this interaction probably is adsorption of nitrofurantoin onto the surface of magnesium trisilicate.

Uricosuric medicines, such as probenecid and sulphapyrazone, 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.

Drug/Laboratory Test Interactions

As a result of the presence of nitrofurantoin, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions but not with the glucose enzymatic test. Antagonism has been demonstrated *in vitro* between nitrofurantoin and quinolone antimicrobials. The clinical significance of this finding is unknown.

4.6 Fertility, pregnancy and lactation

Fertility

Teratogenic effects

Several reproduction studies have been performed in rabbits and rats at doses up to six times the human dose and have revealed no evidence of impaired fertility or harm to the foetus due to nitrofurantoin. In a single published study conducted in mice at 68 times the human dose (based on mg/kg administered to the dam), growth retardation and a low incidence of minor and common malformations were observed. However, at 25 times the human dose, foetal malformations were not observed.

Non-teratogenic effects

Nitrofurantoin has been shown in one published transplacental carcinogenicity study to induce lung papillary adenomas in the F1 generation mice at doses 19 times the human dose on a mg/kg basis.

Pregnancy

Category A (short term therapy): Medicines that have been taken by a large number of pregnant women and women of childbearing age without any proven increase in

the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

Caution should be exercised when administering nitrofurantoin at term because of the possibility of producing haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and due to immature enzyme systems in the early neonatal period (see also section 4.3 Contraindications).

Breastfeeding

Nitrofurantoin has been detected in human breast milk in trace amounts. Because of the potential for serious adverse reactions from nitrofurantoin in nursing infants under one month of age, a decision should be made whether to discontinue nursing or to discontinue the medicine, taking into account the importance of the medicine to the mother (see section 4.3 Contraindications.)

4.7 Effects on ability to drive and use machines

Nitrofurantoin does not interfere with the ability to drive or use machines.

4.8 Undesirable effects

The most common clinical adverse events reported with use of nitrofurantoin are nausea, headache, and flatulence. Additional less common clinical adverse events reported include:

Gastrointestinal

Diarrhoea, dyspepsia, abdominal pain, constipation, emesis, sialadenitis, pancreatitis.

Neurologic

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 per minute or clinically significant elevated serum creatinine), anaemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency, and debilitating diseases may increase the possibility of peripheral neuropathy (see section 4.4 Special warnings and precautions for use). Asthenia, vertigo, dizziness, drowsiness, amblyopia, and nystagmus also have been reported with the use of nitrofurantoin. Confusion, depression, benign intracranial hypertension, and psychotic reactions have been reported rarely.

Allergic

Pruritus, urticaria, lupus-like syndrome associated with pulmonary reaction to nitrofurantoin has been reported. Also, angioedema; maculopapular, erythematous, or eczematous eruptions; anaphylaxis; arthralgia; myalgia; drug fever; and chills have been reported.

Dermatologic

Alopecia, exfoliative dermatitis and erythema multiforme (including Stevens-Johnson Syndrome) have been reported rarely.

Respiratory

Chronic, subacute, or acute pulmonary hypersensitivity reactions may occur with the use of nitrofurantoin.

Chronic pulmonary reactions generally occur in patients who have received continuous treatment for six months or longer. Malaise, dyspnoea on exertion, cough, and altered pulmonary function are common manifestations which can occur insidiously. Radiologic and histologic findings of diffuse interstitial pneumonitis or fibrosis, or both, are also common manifestations of the chronic pulmonary reaction. Fever is rarely prominent.

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.

Acute pulmonary reactions are commonly manifested by fever, chills, cough, chest pain, dyspnoea, pulmonary infiltration with consolidation or pleural effusion on x-ray, and eosinophilia. Acute reactions usually occur within the first week of treatment and are reversible with cessation of therapy. Resolution often is dramatic (see section 4.4 Special warnings and precautions for use.)

In subacute pulmonary reactions, fever and eosinophilia occur less often than in the acute form. Upon cessation of therapy, recovery may require several months. If the symptoms are not recognised as being drug-related and nitrofurantoin therapy is not stopped, the symptoms may become more severe.

Changes in EKG may occur associated with pulmonary reactions.

Cyanosis has been reported rarely.

Hepatic

Hepatic reactions, including hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic necrosis, occur rarely (see section 4.4. Special warnings and precautions for use.)

Miscellaneous

Fever, chills, malaise. As with other antimicrobial agents, superinfections with resistant organisms, e.g., *Pseudomonas* species or *Candida* species, 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 phosphorus. 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, hemolytic anaemia, thrombocytopenia, megaloblastic anaemia. In most cases, these haematologic abnormalities resolved following cessation of therapy. Aplastic anaemia has been reported rarely.

Paediatric population

No information available.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Occasional incidents of acute overdosage of nitrofurantoin have not resulted in any specific symptoms other than vomiting. Induction of emesis is recommended. There is no specific antidote, but a high fluid intake should be maintained to promote urinary excretion of the medicine. Nitrofurantoin is dialysable.

For advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nitrofurantoin derivatives – ATC code: J01XE01.

Microbiology

Nitrofurantoin is bactericidal in urine at therapeutic doses. The mechanism of the antimicrobial action of nitrofurantoin is unusual among antibacterials. Nitrofurantoin is reduced by bacterial flavoproteins to reactive intermediates which inactivate or alter bacterial ribosomal proteins and other macromolecules. As a result of such inactivations, the vital biochemical processes of protein synthesis, aerobic energy metabolism, DNA synthesis, RNA synthesis, and cell wall synthesis are inhibited. The broad-based nature of this mode of action may explain the lack of acquired bacterial resistance to nitrofurantoin, as the necessary multiple and simultaneous mutations of the target macromolecules would likely be lethal to the bacteria. Development of resistance to nitrofurantoin has not been a significant problem since its introduction in 1953. Cross-resistance with antibiotics and sulfonamides has not been observed, and transferable resistance is, at most, a very rare phenomenon.

Nitrofurantoin has been shown to be active against most strains of the following bacteria:

Gram-Positive Aerobes:

- Coagulase-negative *staphylococci* (including *Staphylococcus epidermidis*)
- *Enterococcus faecalis*
- *Staphylococcus saprophyticus*
- *Staphylococcus aureus*
- *Streptococcus agalactiae*
- Group D *streptococci*
- Viridans group *streptococci*

Gram-Negative Aerobes:

- *Escherichia coli*
- *Citrobacter amalonaticus*
- *Citrobacter diversus*
- *Citrobacter freundii*
- *Klebsiella oxytoca*
- *Klebsiella ozaenae*

Nitrofurantoin is not active against most strains of *Proteus* species or *Serratia* species. It has no activity against *Pseudomonas* species.

Susceptibility Tests

Diffusion Techniques

Quantitative methods that require measurement of zone diameters give the most precise estimate of the susceptibility of bacteria to antimicrobial agents. One such standard procedure, which has been recommended for use with disks to test susceptibility of organisms to nitrofurantoin, uses the 300 mcg nitrofurantoin disk. Interpretation involves the correlation of the diameter obtained in the disk test with the minimum inhibitory concentration (MIC) for nitrofurantoin.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 300 mcg nitrofurantoin disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥17	Susceptible
15-16	Intermediate
≤14	Resistant

A report of "susceptible" indicates that the pathogen is likely to be inhibited by generally achievable urinary levels. A report of "intermediate" indicates that the result be considered equivocal and, if the organism is not fully susceptible to alternative clinically feasible medicines, the test should be repeated. This category provides a buffer zone, which prevents small, uncontrolled technical factors from causing major discrepancies in interpretations. A report of "resistant" indicates that achievable concentrations are unlikely to be inhibitory, and other therapy should be selected.

Standardised procedures require the use of laboratory control organisms. The 300 mcg nitrofurantoin disk should give the following zone diameters:

Organism	Zone Diameter (mm)
<i>E. coli</i> ATCC 25922	20-25
<i>S. aureus</i> ATCC 25923	18-22

Dilution Techniques

Use a standardised dilution method (broth, agar, microdilution) or equivalent with nitrofurantoin powder. The MIC values obtained should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤32	Susceptible
64	Intermediate
≥128	Resistant

As with standard diffusion techniques, dilution methods require the use of laboratory control organisms. Standard nitrofurantoin powder should provide the following MIC values:

Organism	MIC (mcg/mL)
<i>E. coli</i> ATCC 25922	4-16
<i>S. aureus</i> ATCC 29213	8-32
<i>E. faecalis</i> ATCC 29212	4-16

5.2 Pharmacokinetic properties

Orally administered, all dosage forms of nitrofurantoin are readily absorbed and rapidly excreted in urine. Plasma concentrations at therapeutic dosage are low. The presence of food or agents which delay gastric emptying can increase the bioavailability of nitrofurantoin by up to 40%.

5.3 Preclinical safety data

Nitrofurantoin was not carcinogenic when fed to female Holtzman rats for 44.5 weeks or to female Sprague-Dawley rats for 75 weeks. Two chronic rodent bioassays utilising male and female Sprague-Dawley rats and two chronic bioassays in Swiss mice and in BDF1 mice revealed no evidence of carcinogenicity.

Nitrofurantoin presented evidence of carcinogenic activity in female B6C3F1 mice as shown by increased incidences of tubular adenomas, benign mixed tumors, and granulosa cell tumors of the ovary. In male F344/N rats, there was an increased incidence of uncommon kidney tubular cell neoplasms, osteosarcomas of the bone, and neoplasms of the subcutaneous tissue. In one study involving subcutaneous administration of 75 mg/kg nitrofurantoin to pregnant female mice, lung papillary adenomas of unknown significance were observed in the F1 generation.

Nitrofurantoin has been shown to induce point mutations in certain strains of *Salmonella typhimurium* and forward mutations in L5178Y mouse lymphoma cells. Nitrofurantoin induced increased numbers of sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells but not in human cells in culture. Results of the sex-linked recessive lethal assay in *Drosophila* were negative after administration of nitrofurantoin by feeding or by injection. Nitrofurantoin did not induce heritable mutation in the rodent models examined.

The significance of the carcinogenicity and mutagenicity findings relative to the therapeutic use of nitrofurantoin in humans is unknown.

The administration of high doses of nitrofurantoin to rats causes temporary spermatogenic arrest; this is reversible on discontinuing the medicine. Doses of 10 mg/kg/day or greater in healthy human males may, in certain unpredictable instances, produce a slight to moderate spermatogenic arrest with a decrease in sperm count.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acacia
Alginic acid
Lactose monohydrate
Magnesium stearate
Maize starch
Sodium laurilsulfate
Sucrose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Bottles of 100 tablets.

6.6 Special precautions for disposal and other handling

No special requirements for disposal. Any used medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

WM Bamford & Company Limited
12 Victoria Street
Private Bag 31346
LOWER HUTT 5040

Phone: (04) 576 2100
Fax: (04) 569 6489

9. DATE OF FIRST APPROVAL

31 December 1969.

10. DATE OF REVISION OF THE TEXT

10 July 2017.

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All sections	Adoption of the new Medsafe Data Sheet SmPC-style format and content requirements according to NZDS Explanatory Guide, effective 1 March 2017.