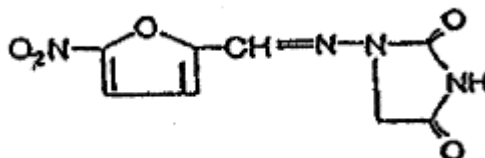


# PRODUCT INFORMATION

## MACRODANTIN<sup>®</sup> capsules 50 mg and 100 mg (nitrofurantoin macrocrystals)

### NAME OF THE MEDICINE

Nitrofurantoin has the following chemical structure:



Nitrofurantoin has the following molecular formula, molecular weight and Chemical Abstracts Service (CAS) Registry number: C<sub>8</sub>H<sub>6</sub>N<sub>4</sub>O<sub>5</sub>, 238.2, CAS-67-20-9.

### DESCRIPTION

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. In view of this, the drug should be dispensed in amber coloured bottles.

**Note:** MACRODANTIN (nitrofurantoin macrocrystals) is a larger crystal form of nitrofurantoin. The absorption of MACRODANTIN is slower and the excretion of MACRODANTIN is somewhat less, when the two are compared. The reduced incidence of gastrointestinal intolerance with MACRODANTIN is probably due to delayed and decreased absorption; this however does not significantly reduce clinical effectiveness. A number of patients who cannot tolerate nitrofurantoin tablets can take MACRODANTIN capsules without nausea.

### PHARMACOLOGY

#### Microbiology

MACRODANTIN 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 *E. coli*, 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
<i>Staph aureus</i>	4 - 30
<i>Str pyogenes</i>	10
<i>Str viridans</i>	8
<i>Str faecalis</i>	4 - 125
<i>N gonorrhoeae</i>	15
<i>Esch coli</i>	0.4 - >250
<i>Proteus spp</i>	7.5 - >200
<i>Klebsiella-Aerobacter spp</i>	25 - >200
<i>Salmonella spp</i>	5-15
<i>Shigella spp</i>	5
<i>Ps aeruginosa</i>	>200

Urine levels reached with normal therapeutic doses are usually in the range of 15-46 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.

### Pharmacokinetics

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.

### 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.

### 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.

## **PRECAUTIONS**

### **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 ADVERSE REACTIONS - 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 ADVERSE REACTIONS - 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 ADVERSE REACTIONS - Pulmonary hypersensitivity).

### **Impaired Renal Function or Acidosis**

In the presence of impairment of renal function or acidosis, administer MACRODANTIN with caution. If employed under such circumstances the blood pH, CO<sub>2</sub> 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.

### **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.

### **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.

### **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.

### **Mutagenicity**

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.

### **Genotoxicity**

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.

### **Use in 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 During 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.

### **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.

## **INTERACTIONS WITH OTHER MEDICINES**

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.

## **ADVERSE 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 PRECAUTIONS), 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

## **DOSAGE AND 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.

## **OVERDOSAGE**

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.

Contact the Poisons Information Centre for advice on the management of an overdose.

## **PRESENTATION AND STORAGE CONDITIONS**

50 mg capsules (yellow/white, marked EATON 008): HDPE bottles of 4 and 30;

100 mg capsules (yellow, marked EATON 009): HDPE bottles of 30.

Excipients: maize starch, purified talc, lactose, gelatin, titanium dioxide, quinoline yellow CI47005, sodium lauryl sulfate, black printing ink (Tekprint SW-9008, Tekprint SW-9010).

Store below 30°C.

## **SPONSOR NAME AND ADDRESS**

Pfizer Australia Pty Ltd  
ABN 50 008 422 348  
38-42 Wharf Road  
West Ryde NSW 2114

## **POISON SCHEDULE**

S4, Prescription Only Medicine

## **DATE OF FIRST INCLUSION ON THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)**

29 May 1997



## **DATE OF MOST RECENT AMENDMENT**

**7 May 2013**

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