New Zealand Data Sheet

1 PRODUCT NAME

Macrobid 100mg Modified-release Capsules.

Nitrofurantoin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Macrobid is a modified release, hard gelatin capsule containing the equivalent of 100mg of Nitrofurantoin in the form of nitrofurantoin macrocrystals and nitrofurantoin monohydrate.

Pharmacotherapeutic group: Urinary Anti-infectives

ATC Code: J01XE01

3 PHARMACEUTICAL FORM

Macrobid is available as 100 mg opaque black and yellow modified-release capsules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Macrobid is indicated for the treatment of acute uncomplicated urinary tract infections (acute cystitis) caused by susceptible strains of Escherichia coli or Staphylococcus saprophyticus. Therapy with Macrobid 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.

Macrobid is indicated for the prophylaxis of urinary tract infections after surgery or procedures involving genitourinary tract.

Macrobid is not indicated for the treatment of pyelonephritis or perinephric abscesses.

4.2 Dose and method of administration

Acute, Uncomplicated Urinary Tract Infections (acute cystitis)
Macrobid capsules should be taken with food.

Adults and Paediatric Patients Over 12 Years:

One 100 mg capsule every 12 hours for seven days.

Prophylactic Therapy
Adults and Paediatric Patients Over 12 Years:

One 100 mg capsule every 12 hours for three days.

First dose is to be given immediately before surgery or procedure.

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 drug.

Because of the possibility of haemolytic anemia due to immature erythrocyte enzyme systems (glutathione instability), the drug is contraindicated in pregnant patients at term (38- 42 weeks gestation), during labour and delivery, or when the onset of labour is imminent. For the same reason, the drug is contraindicated in neonates under one month of age.

Macrobid is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with nitrofurantoin.

Macrobid is also contraindicated in those patients with known hypersensitivity to nitrofurantoin.

4.4 Special warnings and precautions for use

Pulmonary reactions:

Acute, sub-acute or chronic pulmonary reactions have been observed in patients treated with nitrofurantoin. If these reactions occur, Macrobid should be discontinued, and appropriate measures take. 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 Respiratory reactions).

Hepatotoxicity:

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 biochemical tests that would indicate liver injury. If hepatitis occurs, the drug should be withdrawn immediately, and appropriate measures should be taken.

Neuropathy:

Peripheral neuropathy, 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.

Optic neuritis has been reported rarely in post-marketing experience with nitrofurantoin formulations.

Haemolytic anemia:
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. This deficiency is found in 10 percent of Blacks and a small percentage of ethnic groups of Mediterranean and Near- Eastern origin. Haemolysis is an indication for discontinuing Macrobid; haemolysis ceases when the drug is withdrawn.

Clostridium difficile-associated diarrhoea:
Clostridium difficile-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including nitrofurantoin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS:
Information for Patients:
Patients should be advised to take Macrobid with food (ideally breakfast and dinner) to further enhance tolerance and improve drug 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 while taking Macrobid.

Patients should be counselled that antibacterial drugs including Macrobid should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Macrobid are prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may

(1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Macrobid or other antibacterial drugs in the future.

Diarrhoea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Paediatric Use:
Macrobid are contraindicated in infants below the age of one month. (See contraindications). Safety and effectiveness in paediatric patients below the age of twelve years have not been established.

Geriatric Use:
Clinical studies of Macrobid did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Spontaneous reports suggest a higher proportion of pulmonary reactions, including fatalities, in elderly patients; these differences appear to be related to the higher proportion of elderly patients receiving long- term nitrofurantoin therapy.

As in younger patients, chronic pulmonary reactions generally are observed in patients receiving therapy for six months or longer (see Warnings). Spontaneous reports also suggest an increased proportion of severe hepatic reactions, including fatalities, in elderly patients (see Warnings).

In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing Macrobid. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine) are contraindications (see Contraindications). Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

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 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.

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.

4.6 Fertility, pregnancy and lactation

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

Use in Pregnancy
Teratogenic effects:
Pregnancy Category B. 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; the relevance of these findings to humans is uncertain. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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. The relationship of this finding to potential human carcinogenesis is presently unknown. Because of the uncertainty regarding the human implications of these animal data, this drug should be used during pregnancy only if clearly needed.

Studies in pregnant women have not shown that nitrofurantoin increases the risk of foetal abnormalities if administered during any trimester of pregnancy. If this drug is used during pregnancy, the possibility of foetal harm due to nitrofurantoin appears remote.

Use in Lactation
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 drug, taking into account the importance of the drug to the mother. (See 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

In clinical trials of Macrobid, the most frequent clinical adverse events that were reported as possibly or probably drug-related were nausea (8%), headache (6%), and flatulence (1.5%). Additional clinical adverse events reported as possibly or probably drug-related occurred in less than 1% of patients studied and are listed below within each body system in order of decreasing frequency:

Gastrointestinal: Diarrhea, dyspepsia, abdominal pain, constipation, emesis Neurologic: Dizziness, drowsiness, amblyopia

Respiratory: Acute pulmonary hypersensitivity reaction (see Warnings) Allergic: Pruritus, urticaria

Dermatologic: Alopecia

Miscellaneous: Fever, chills, malaise

The following additional clinical adverse events have been reported with the use of nitrofurantoin:

Gastrointestinal:
Sialadenitis, pancreatitis. There have been sporadic reports of pseudomembranous colitis with the use of nitrofurantoin. The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment. (See Warnings).

Neurologic:
Peripheral neuropathy, 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 diseases may increase the possibility of peripheral neuropathy. (See Warnings). Asthenia, vertigo, and nystagmus also have been reported with the use of nitrofurantoin.

Benign intracranial hypertension (pseudotumor cerebri), confusion, depression, optic neuritis, and psychotic reactions have been reported rarely. Bulging fontanels, as a sign of benign intracranial hypertension in infants, 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 recognized early.

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 recognized as being drug-related and nitrofurantoin therapy is not stopped, the symptoms may become more severe.

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 Warnings).

Changes in EKG (e.g., non-specific ST/T wave changes, bundle branch block) have been reported in association with pulmonary reactions.

Cyanosis has been reported rarely.

Hepatic:
Hepatic reactions, including hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic necrosis occur rarely (See Warnings).

Allergic:
Lupus-like syndrome associated with pulmonary reaction to nitrofurantoin has been reported. Also, angioedema; maculopapular, erythematous, or eczematous eruptions; anaphylaxis; arthralgia; myalgia; drug fever; chills; and vasculitis (sometimes associated with pulmonary reactions) have been reported. Hypersensitivity reactions represent the most frequent spontaneously-reported adverse events in worldwide post-marketing experience with nitrofurantoin formulations.

Dermatologic:
Exfoliative dermatitis and erythema multiforme (including Stevens-Johnson syndrome) have been reported rarely.

Hematologic:
Cyanosis secondary to methemoglobinemia has been reported rarely.

Miscellaneous:
As with other antimicrobial agents, superinfections caused by resistant organisms, e.g., Pseudomonas species or Candida species, can occur.

In clinical trials of Macrobid, the most frequent laboratory adverse events (1-5%), without regard to drug relationship, were 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 anemia (see Warnings), agranulocytosis, leukopenia, granulocytopenia, haemolytic anemia, thrombocytopenia, megaloblastic anemia. In most cases, these hematologic abnormalities resolved following cessation of therapy. Aplastic anemia has been reported rarely.

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

Nitrofurantoin is a nitrofuran antimicrobial agent with activity against certain Gram positive and Gram-negative bacteria.

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. Nitrofurantoin is bactericidal in urine at therapeutic doses. 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 sulphonamides 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 both in vitro and in clinical infections [see Indication):

Aerobic and facultative Gram-positive microorganisms:
Staphylococcus saprophyticus

Aerobic and facultative Gram-negative microorganisms:
Escherichia coli

At least 90 percent of the following microorganisms exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for nitrofurantoin.

However, the efficacy of nitrofurantoin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled trials.

Aerobic and facultative Gram-positive microorganisms:
Coagulase-negative staphylococci (including Staphylococcus epidermidis)
Enterococcus faecalis
Staphylococcus aureus
Streptococcus aga/actiae
Group D streptococci
Viridans group streptococci

Aerobic and facultative Gram-negative microorganisms:
Citrobacter ama/onaticus
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 Test Methods:
When available, the clinical microbiology laboratory should provide cumulative results of the in vitro susceptibility test results for antimicrobial drugs used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution techniques:
Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of nitrofurantoin powder. The MIC values should be interpreted according to the criteria provided in Table 1.

Diffusion technique:
Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 300 µg of nitrofurantoin to test the susceptibility of microorganisms to nitrofurantoin. The disk diffusion interpretive criteria are provided in Table 1.

Table 1. Susceptibility Interpretive Criteria for Nitrofurantoin

	Susceptibility Interpretive Criteria

Pathogen	Minimum Inhibitory Concentrations (µg/mL)			Disk Diffusion (zone diameter in mm)		
	S	I	R	S	I	R
Enterobacteriaceae	δ32	64	ε128	ε17	15-16	δ14
Staphylococcus spp.	δ32	64	ε128	ε17	15-16	δ14

A report of Susceptible indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the urine reaches the concentrations usually achievable. A report of Intermediate indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone, which prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of Resistant indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the urine reaches the concentrations usually achievable; other therapy should be selected.

Quality Control:
Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard nitrofurantoin powder should provide the following range of values noted in Table 2.

Table 2. Acceptable Quality Control Ranges for Nitrofurantoin

QC Strain	**Acceptable Quality Control Ranges**	
	Minimum Inhibitory Concentration (µg/mL)	Disk Diffusion (zone diameter in mm)
Escherichia coli ATCC 25922	4 – 16	20 -25
Enterococcus faecalis ATCC 29212	4 – 16	NA*
Staphylococcus aureus ATCC 29213	8 – 32	NA*
Staphylococcus aureus ATCC 25923	NA*	18-22

*Not applicable

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%.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each capsule contains carbomer 934P, corn starch, compressible sugar, D&C Yellow No. 10, FD&C Blue No. 1, FD&C Red No. 40, gelatin, lactose, magnesium stearate, povidone, talc, and titanium dioxide. CONTAINS LACTOSE.

6.2 Incompatibilities

None

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25ºC.

6.5 Nature and contents of container

Macrobid is available as 100 mg opaque black and yellow modified-release capsules in a bottle of 100.

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR DETAILS

Te Arai BioFarma Limited
PO Box 46205
Herne Bay Auckland 1011

0800 TE ARAI (83 2724)

9 DATE OF FIRST APPROVAL

1 October 2020

10 DATE OF REVISION OF THE TEXT

19 April 2022

Section Changed	Summary of New Information
3.	Update to capsule appearance, removing printing.
6.1	Removal of edible grey ink from excipient list