

## New nitrofurantoin modified release formulation (Macrobid® 100mg capsules)

First choice for empiric treatment of lower urinary tract infections (UTIs) in adults

- Nitrofurantoin 100mg modified release capsules (Macrobid) are now registered and funded in New Zealand.
- Macrobid is dosed twice daily to treat acute lower UTIs in adults, and is now our first choice for empiric treatment.
- Nitrofurantoin 50mg or 100mg immediate release tablets (Nifuran) will now have limited use in adults, mainly for short-term prophylaxis of UTIs in selected patients.
- This bulletin outlines the role of both nitrofurantoin products in adult UTI management along with important safety considerations related to product selection and toxicity.

### NITROFURANTOIN MODIFIED RELEASE CAPSULES

- We now have two funded formulations of nitrofurantoin:
  - immediate release tablets (Nifuran 50mg and 100mg),
  - modified release capsules (Macrobid 100mg).
- Nitrofurantoin dissolution in the gastrointestinal (GI) tract is slower from Macrobid than from Nifuran enabling twice daily dosing for UTI treatment and potentially better GI tolerability. Macrobid has been available overseas for decades, and is a first choice treatment for acute lower UTI in adults in the USA<sup>1</sup>.
- In Canterbury, nitrofurantoin modified release capsules are now first-choice for empiric treatment of lower UTIs in adults (replacing the immediate release tablets that require four times daily dosing)<sup>2</sup>. Nitrofurantoin immediate release tablets are the preferred choice if prophylaxis of UTIs is indicated (see below)<sup>3</sup>.

### ROLE OF NITROFURANTOIN IN LOCAL UTI GUIDELINES

#### *Escherichia coli* susceptibility

- Most acute lower UTIs (75 – 95%) are caused by *E. coli*, which are highly susceptible to nitrofurantoin (99%)<sup>4</sup>. This includes strains that produce extended-spectrum  $\beta$ -lactamases (92%)<sup>5</sup>.
- Nitrofurantoin kills bacteria via multiple mechanisms which may partly explain why *E. coli* susceptibility to nitrofurantoin remains high compared with other agents used to treat UTIs:

#### *E. coli* susceptibility in urinary samples at CHL (2019)<sup>4</sup>

Nitrofurantoin	99%
Cefalexin	92%
Ciprofloxacin	90%
Trimethoprim + sulfamethoxazole	79%
Trimethoprim	76%
Amoxicillin + clavulanic acid	70%
Amoxicillin	55%

### Empiric treatment of lower UTIs

- CDHB [Pink Book](#)<sup>2</sup> guidelines (HealthPathways will be updated to align) for empiric treatment of lower UTI in non-pregnant women now recommend (in order):
  1. Nitrofurantoin PO 100mg (modified release) twice daily for 5 days
  2. Cefalexin PO 500mg twice daily for 5 days
  3. Trimethoprim PO 300mg once daily for 3 daysIn pregnancy, cefalexin is first-line, nitrofurantoin is second-line (not when labour is imminent) and trimethoprim is third-line (not in the first-trimester). In men, empiric treatment is the same as for non-pregnant women but the course is extended to 7 days<sup>2</sup>.
- Choice of agents in our empiric guidelines reflects susceptibility patterns plus antimicrobial stewardship considerations such as ability to promote resistance, tolerability, and compliance.
- **Nitrofurantoin** is first-line as *E. coli* susceptibility is high, and it is well-tolerated, narrow spectrum (helping slow resistance) and is only effective for bladder infections (i.e. use for this relatively

minor indication does not compromise its wider clinical utility). **Cefalexin** is second-line as it is broader spectrum and is used for infections beyond the bladder. **Trimethoprim** is third-line as *E. coli* resistance is high at ~24% of isolates. **Other agents** are not recommended empirically due to high *E. coli* resistance and/or their broader spectrum of antimicrobial activity.

### Prophylaxis of lower UTIs

- [Hospital HealthPathways](#)<sup>3</sup> and [Community HealthPathways](#)<sup>3</sup> provide advice on management of recurrent lower UTIs.
- If prophylaxis with nitrofurantoin is indicated, start with 50mg daily (reserve 100mg daily for inadequate responders). Use immediate release tablets as modified release capsules offer no clinical advantage for prophylaxis. Limit prophylaxis to 3 months initially. Usual maximum duration is 6 months.

### NITROFURANTOIN SAFETY CONCERNS – HIGHLIGHTS

- **Do not use nitrofurantoin for infections beyond the bladder** as blood and tissue concentrations are too low with standard oral dosing to treat infections at other sites.
- **Do not use nitrofurantoin if creatinine clearance < 30 mL/min** as good renal function is needed for effective nitrofurantoin urine concentrations, and to avoid high blood concentrations that increase toxicity. If creatinine clearance is 30 – 60 mL/min, consult Infectious Diseases/Microbiology before use as a short-course may sometimes be acceptable (e.g. multiresistant UTIs).
- **Monitor for nitrofurantoin toxicity.** Serious adverse effects involving the lungs, liver or nervous system may occur with short or long-term use. Prescribers should familiarise themselves with these and ensure prompt cessation of nitrofurantoin at first sign of toxicity. See: [Medsafe nitrofurantoin article](#)<sup>6</sup>.
- **Minimise potential for error with product selection.** Refer to the new product as “nitrofurantoin modified release” or Macrobid.
- **Recommend that nitrofurantoin is taken with food** to optimise oral availability.

### MACROBID®: 90 DAY “IN USE” SHELF-LIFE & PRODUCT LABELLING

- Macrobid product labelling does **not** state that it is modified release (compared with Nifuran) nor that it has a 90 day “in use” shelf-life (the latter is stated in the current Macrobid [datasheet](#))<sup>7</sup>.
- Work is underway to extend the “in use” shelf-life to the full expiry date if possible. Meanwhile, PHARMAC has enabled pharmacies to “claim wastage” of unused stock after 90 days (to be reviewed in the future). Please rotate stock appropriately and keep a look out for new information on the “in use” shelf-life.

#### References:

1. Hooton TM, Gupta K. [Acute simple cystitis in women](#). [www.uptodate.com](#) (accessed 02.02.21)
2. Pink Book Antimicrobial Guidelines. <https://www.pinkbook.org.nz/>
3. 'Lower UTIs in Women' [Hospital HealthPathways](#), [Community HealthPathways](#) (also see pathways for 'Lower UTIs in Men')
4. [Canterbury Health Laboratories Antimicrobial Susceptibility Patterns 2019](#)
5. Creighton JA. *N Z J Med Lab Sci* 2014; 68: 19-23
6. [Spotlight on nitrofurantoin](#). Medsafe, Wellington, NZ (accessed 02.02.21)
7. <https://www.medsafe.govt.nz/profs/Datasheet/m/macrobidcap.pdf>