

**1. NAME OF THE MEDICINAL PRODUCT**

Macrobid 100mg Capsules.

**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.

**3. PHARMACEUTICAL FORM**

The 100mg capsule has an opaque blue cap and opaque yellow body and bears the monogram "GS 100".

**4. CLINICAL PARTICULARS**

**4.1. Therapeutic indications**

For the treatment of and prophylaxis against acute or recurrent, uncomplicated lower urinary tract infections or pyelitis either spontaneous or following surgical procedures.

Macrobid is specifically indicated for the treatment of infections when due to susceptible strains of Escherichia coli, Enterococci, Staphylococci, Citrobacter, Klebsiella and Enterobacter.

Most strains of Proteus and Serratia are resistant. All Pseudomonas strains are resistant.

Macrobid is not indicated for the treatment of associated renal cortical or perinephric abscesses.

**4.2. Posology and method of administration**

Route of administration: Oral

Adults and children over 12 years of age.

The dose should be taken with food or milk (e.g. at meal times).

Acute or recurrent uncomplicated UTI and pyelitis -100mg twice daily for seven days.

Surgical Prophylaxis - 100 mg twice daily on the day of the procedure and 3 days thereafter.

### Elderly

Provided there is no significant renal impairment, in which nitrofurantoin is contraindicated, the dosage should be that for any normal adult.

See precaution and risks to elderly patients associated with long term therapy.

### Children under 12 years

Macrobid is a fixed dosage and is therefore not suitable for children under 12 years

## **4.3 Contraindications**

Patients with known hypersensitivity to nitrofurantoin or other nitrofurans.

Patients suffering from renal dysfunction with a creatinine clearance of less than 60 ml/minute or elevated serum creatinine.

G6PD deficiency (see also Section 4.6)

Acute porphyria.

In infants under three months of age as well as pregnant patients at term (during labour and delivery) because of the theoretical possibility of haemolytic anaemia in the foetus or in the newborn infant due to immature erythrocyte enzyme systems.

## **4.4 Special warnings and precautions for use**

Nitrofurantoin is not effective for the treatment of parenchymal infections of a unilaterally functioning kidney. A surgical cause for infection should be excluded in recurrent or severe cases.

Since pre-existing conditions may mask hepatic or pulmonary adverse reactions, nitrofurantoin should be used with caution in patients with pulmonary disease, hepatic dysfunction, neurological disorders and allergic diathesis.

Peripheral neuropathy and susceptibility to peripheral neuropathy, which may become severe or irreversible has occurred and may be life threatening. Therefore, treatment should be stopped at the first signs of neural involvement (paraesthesiae).

Nitrofurantoin should be used with caution in patients with anaemia, diabetes mellitus, electrolyte imbalance, debilitating conditions, and vitamin B (particularly folate) deficiency.

Acute, subacute and chronic pulmonary reactions have been observed in patients treated with nitrofurantoin. If these reactions occur, nitrofurantoin should be discontinued immediately.

Chronic pulmonary reactions (including pulmonary fibrosis and diffuse interstitial pneumonitis ) can develop insidiously, and may occur commonly in elderly patients. Close monitoring of the pulmonary conditions of patients receiving long-term therapy is warranted (especially in the elderly).

Patients should be monitored closely for signs of hepatitis (particularly in long term use).

Urine may be coloured yellow or brown after taking Nitrofurantoin. Patients on Nitrofurantoin are susceptible to false positive urinary glucose (if tested for reducing substances).

Nitrofurantoin should be discontinued at any signs of haemolysis in those with suspected glucose-6-phosphate dehydrogenase deficiency.

Gastrointestinal reactions may be minimised by taking the drug with food or milk, or by adjustment of dosage.

For long term treatment monitor the patient closely for appearance of hepatic or pulmonary symptoms and other evidence of toxicity.

Discontinue treatment with nitrofurantoin if otherwise unexplained pulmonary, hepatotoxic, haematological or neurological syndromes occur.

#### **4.5 Interactions with other medicaments and other forms of interaction**

1. Increased absorption with food or agents delaying gastric emptying.
2. Decreased absorption with magnesium trisilicate.
3. Decreased renal excretion of Nitrofurantoin by probenecid and Sulphinpyrazone.
4. Decreased anti-bacterial activity by carbonic anhydrase inhibitors and urine alkalinisation.

5. Anti-bacterial antagonism by quinolone anti-infectives.
6. Interference with some tests for glucose in urine.
7. As Nitrofurantoin belongs to a group of anti-bacterials and will have the following interactions:  
Oestrogens: In common with other antibiotics, nitrofurantoin may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of oestrogen-containing contraceptive products. Therefore, patients should be warned appropriately and extra contraceptive precautions taken.  
  
Typhoid vaccine (oral): Antibacterials inactivate oral typhoid vaccine.

#### **4.6. Pregnancy and lactation**

Animal studies with nitrofurantoin have shown no teratogenic effects. Nitrofurantoin has been in extensive clinical use since 1952 and its suitability in human pregnancy has been well documented. However, as with all other drugs, the maternal side effects may adversely affect course of pregnancy. The drug should be used at the lowest dose as appropriate for a specific indication, only after careful assessment.

Nitrofurantoin is however contraindicated in infants under three months of age and in pregnant women during labour and delivery because of the possible risk of haemolysis of the infants immature red cells. Breast feeding an infant known or suspected to have an erythrocyte enzyme deficiency (including G6PD deficiency), must be temporarily avoided, since Nitrofurantoin is detected in trace amounts in breast milk.

#### **4.7 Effects on ability to drive and use machines**

Macrobid may cause dizziness and drowsiness. Patients should be advised not to drive or operate machinery if affected in this way until such symptoms go away.

#### **4.8 Undesirable effects**

##### **Respiratory**

If any of the following respiratory reactions occur the drug should be discontinued.

**Acute pulmonary reactions** usually occur within the first week of treatment and are reversible on cessation of therapy. Acute pulmonary reactions are commonly manifested by fever, chills, cough, chest pain, dyspnoea, pulmonary infiltration with consolidation or pleural effusion on chest x-ray, and eosinophilia. In subacute pulmonary reactions, fever and eosinophilia occur less often than in the acute form

**Chronic pulmonary reactions** occur rarely in patients who have received continuous therapy for six months or longer and are more common in elderly patients. Changes in ECG have occurred, associated with pulmonary reactions.

Minor symptoms such as fever, chills, cough and dyspnoea may be significant. Collapse and cyanosis have been reported rarely. 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. It is important to recognise symptoms as early as possible. Pulmonary function may be impaired permanently, even after cessation of therapy.

### **Hepatic**

Hepatic reactions including cholestatic jaundice and chronic active hepatitis occur rarely. Fatalities have been reported. Cholestatic jaundice is generally associated with short-term therapy (usually up to two weeks). Chronic active hepatitis, occasionally leading to hepatic necrosis is generally associated with long-term therapy (usually after six months). The onset may be insidious. Treatment should be stopped at the first sign of hepatotoxicity.

### **Neurological**

Peripheral neuropathy (including optical neuritis) with symptoms of sensory as well as motor involvement, which may become severe or irreversible, has been reported infrequently. Less frequent reactions of unknown causal relationship are depression, euphoria, confusion, psychotic reactions, nystagmus, vertigo, dizziness, asthenia, headache and drowsiness. Treatment should be stopped at the first sign of neurological involvement.

### **Gastrointestinal**

Nausea and anorexia have been reported. Emesis, abdominal pain and diarrhoea are less common gastrointestinal reactions.

## **Hypersensitivity**

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

Allergic skin reactions manifesting as angioneurotic oedema, maculopapular, erythematous or eczematous eruptions, urticaria, rash, and pruritus have occurred. Lupus-like syndrome associated with pulmonary reactions to nitrofurantoin has been reported.

Other hypersensitivity reactions include anaphylaxis, sialadenitis, pancreatitis, drug fever and arthralgia.

## **Haematological**

Agranulocytosis, leucopenia, granulocytopenia, haemolytic anaemia, thrombocytopenia, glucose-6-phosphate dehydrogenase deficiency, anaemia, megaloblastic anaemia and eosinophilia have occurred. Cessation of therapy has generally returned the blood picture to normal. Aplastic anaemia has been reported rarely.

## **Other**

Transient alopecia and benign intracranial hypertension.

Superinfections by fungi or resistant organisms such as *Pseudomonas* may occur. However, these are limited to the genito-urinary tract.

## **4.9. Overdose**

Symptoms and signs of overdose include gastric irritation, nausea and vomiting. There is no specific antidote. Nitrofurantoin can be haemodialysed. Standard treatment is by induction of emesis or by gastric lavage in cases of recent ingestion. Monitoring of full blood count, liver function tests and pulmonary function, are recommended. A high fluid intake should be maintained to promote urinary excretion of the drug.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1. Pharmacodynamic properties**

Nitrofurantoin is a broad spectrum antibacterial agent, active against the majority of urinary pathogens. It is bactericidal in renal tissue and throughout the urinary tract. The wide range of organisms sensitive to the bacterial activity include *Escherichia coli*, *Enterococcus faecalis*, *Klebsiella species*, *Enterobacter species*, *Staphylococcus species*: (eg *S. aureus*, *S. saprophyticus*, *S. epidermidis*)

Clinically, most common urinary pathogens are sensitive to nitrofurantoin. Some strains of *Enterobacter* and *Klebsiella* are resistant. Nitrofurantoin is not active against most strains of *Proteus* species or *Serratia* species. It has no activity against *Pseudomonas* species.

### **5.2. Pharmacokinetic properties**

Clinical Pharmacology:

Each Macrobid capsule contains two forms of nitrofurantoin. 25% of the dose is macrocrystalline nitrofurantoin which has slower dissolution and absorption than nitrofurantoin microcrystals. The remaining 75% of the dose is microcrystalline nitrofurantoin contained in a powdered blend which on exposure to gastric and intestinal fluids forms a gel matrix resulting in a modified release of active ingredient over time. Combined these systems provide a clinically effective bactericidal urine concentration at therapeutic doses. Approx. 20-25% of the total single dose of nitrofurantoin is recovered from the urine unchanged over 24 hours.

Plasma nitrofurantoin concentrations at therapeutic doses of the Macrobid capsule are low, with peak levels usually less than 1 mcg/ml. Nitrofurantoin is highly soluble in urine to which it may impart a brown colour. Unlike many drugs the presence of food or agents delaying gastric emptying increases the bioavailability of the Macrobid capsule.

### **5.3. Preclinical safety data**

None stated.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Macrobid Capsules contain talc, corn starch, lactose carbopol, povidone, sugar, magnesium stearate, gelatin, Sodium lauryl sulphate and colouring agents (E104, E171, E132).

Printing ink contains Shellac, Propylene Glycol (E1520), Titanium Dioxide (E171) and Black iron oxide (E172).

### **6.2. Incompatibilities**

None known.

### **6.3. Shelf life**

The expiry date for the product should not exceed 2 years from the date of its manufacture.

### **6.4 Special precautions for storage**

Capsules should be stored in light and moisture resistant containers.  
Storage temperature should not exceed 30°C (aluminium/ aluminium).  
Do not store above 25°C (For PVC/ polyethylene/aclar/aluminium blisters)

### **6.5. Nature and contents of container**

There are two pack sizes, one consists of 14 capsules and the other is a sample pack containing 2 capsules.

### **6.6. Instruction for use and handling, (and disposal)**

A patient information leaflet is provided with the product.

No Data Held

**ADMINISTRATIVE DATA**

**7. MARKETING AUTHORISATION HOLDER**

Goldshield Pharmaceuticals Limited  
NLA Tower  
12-16 Addiscombe Road  
Croydon  
Surrey  
CR0 0XT  
United Kingdom.

**8. MARKETING AUTHORISATION NUMBER**

PL: 12762/0052.

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE  
AUTHORISATION**

31<sup>st</sup> March 2000.

**10 DATE OF REVISION OF THE TEXT**

26/05/2011