

## Summary of Product Characteristics

### 1 NAME OF THE MEDICINAL PRODUCT

MacroBID 100mg Prolonged-Release Capsules

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains the equivalent of 100mg of Nitrofurantoin as the anhydrous form and monohydrate form.

Excipients: each capsule contains lactose monohydrate 194.6 mg and sucrose 31 mg.

For a full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Prolonged release capsule, hard.

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 prophylaxis.

#### 4.2 Posology and method of administration

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 7 days.

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

Long Term Suppressive Therapy - 100mg once a day at bedtime is suggested.

#### Elderly Patients

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

#### Children Under 12 Years Old

MacroBID is a fixed dosage and because of this is unsuitable for children under 12 years old. For children under 12 years old, consideration should be given to the use of Furadantin Suspension.

#### 4.3 Contraindications

Patients with known hypersensitivity to nitrofurantoin or other nitrofurans.

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

G6PD deficiency: May produce neonatal haemolysis if used at term. Only small amounts are present in breast-milk but could be enough to produce haemolysis in G6PD deficient infants.

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 unilaterally non-functioning kidney. A surgical cause for infection should be excluded in recurrent or severe cases and treated accordingly.

Since pre-existing conditions may mask 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 condition of patients receiving long-term therapy is warranted (especially in the elderly).

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 may cause haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency (ten percent of black patients and a variable percentage of ethnic groups of Mediterranean, Near Eastern and Asian origin). Haemolysis ceases when the drug is discontinued.

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

For long term treatment, monitor patient closely for appearance of hepatitis (or liver damage), pulmonary or neurological symptoms and other evidence of toxicity. Discontinue treatment with nitrofurantoin if otherwise unexplained pulmonary, hepatotoxic, haematological or neurologic syndromes occur.

There has been limited evidence of carcinogenic effects of nitrofurantoin in experimental animals, but the drug has not been shown to be carcinogenic in humans.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Concomitant administration of magnesium trisilicate with nitrofurantoin reduces absorption.

Uricosuric drugs such as Probenecid and Sulphinpyrazone may inhibit renal tubular secretion of nitrofurantoin. The resulting increase in serum levels may increase toxicity. Decreased urinary levels could lessen its efficacy as a urinary tract antibacterial.

Concurrent use with quinolones is not recommended.

There may be decreased antibacterial activity for nitrofurantoin in the presence of carbonic anhydrase inhibitors and

urine alkalinising agents.

If tested for reducing substances, false positive urinary glucose. Increased absorption with food or agents delaying gastric emptying.

As Nitrofurantoin belongs to the group of Antibacterials it will have the following resulting interactions:

Oestrogen: Antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, Interactions of combined oral contraceptives may also apply to combined contraceptive patches).

Typhoid Vaccine (oral): Antibacterials inactivate oral typhoid vaccine.

#### **4.6 Fertility, pregnancy and lactation**

Based on animal reproduction studies and clinical experience in humans over many years, there is no evidence of any teratogenic effects of nitrofurantoin on the foetus. Caution should be exercised while breast feeding an infant known or suspected to have any erythrocyte enzyme deficiency as nitrofurantoin is detected in trace amounts in breast milk. Nitrofurantoin is contraindicated in pregnant patients at term (during labour and delivery).

As with all drugs, maternal side effects, should they occur, may adversely affect the course of the pregnancy. The drug should be used at the lowest effective dose only after careful assessment of the benefits against potential risks.

#### **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 with 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.

Subacute reactions may take several months to resolve once the drug has been stopped. 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. Pulmonary fibrosis; possible association with lupus-erythematosus-like syndrome.

##### *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. Rarely liver failure (which may be fatal) have been reported after nitrofurantoin usage.

*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.

*Haematological*

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

*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 pruritis have occurred. Lupus-like syndrome associated with pulmonary reaction to nitrofurantoin has been reported. Other hypersensitivity reactions include anaphylaxis, sialadenitis, pancreatitis, drug fever and arthralgia.

*Other*

Transient alopecia and benign intracranial hypertension. As with other antimicrobial agents, superinfections by fungi or resistant organisms such as *Pseudomonas* may occur.

However, these are limited to the genitourinary tract because suppression of normal bacterial flora does not occur elsewhere in the body.

**4.9 Overdose**

Symptoms and signs of overdosage include gastric irritation, nausea and vomiting. There is no known 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 tract pathogens. The mechanism of action of nitrofurantoin is based on reduction to reactive intermediates. These inhibit enzymes involved in energy metabolism, such as in the Krebs cycle, interfering with the energy supply for normal growth and maintenance of bacteria. They also bind to bacterial ribosomal proteins at different sites, resulting in disruption of bacterial protein synthesis. Transferable resistance to nitrofurantoin is a rare phenomenon. There is no cross resistance to antibiotics and sulphonamides.

**5.2 Pharmacokinetic properties**

Nitrofurantoin is readily absorbed in the upper gastrointestinal tract. Intake with food or milk increases absorption. Nitrofurantoin is highly soluble in urine but plasma concentrations are low with peak levels usually less than 1 mcg/ml.

Nitrofurantoin is loosely bound to plasma albumin (60-70 %). The molecule is readily distributed into intra and extracellular compartments. However, substantial tissue concentrations are not expected since the drug is rapidly excreted and readily degraded by tissue enzymes. The drug crosses the placenta in small amounts.

The elimination half life in blood or plasma after IV injection is about 20 minutes; and after oral administrations of macrocrystals, less than 60 minutes. Following a single dose of nitrofurantoin about 25% is found unchanged in the urine over 24 hours.

### **5.3 Preclinical safety data**

None

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Talc  
Maize starch  
Lactose Monohydrate  
Carbomer  
Povidone  
Sucrose  
Magnesium stearate

#### Capsule shell

Gelatin  
Sodium laurilsulfate  
Quinoline yellow (E104)  
Titanium dioxide (E171)  
Indigo carmine (E132)

#### Printing Ink includes

Shellac  
Propylene glycol (E1520)  
Black iron oxide (E172)  
Titanium dioxide (E171)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

2 years.

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

Do not store above 25°C. Store in original package in order to protect from light.

### **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 in either aluminium/aluminium foil blisters or PVC/PE/Aclar/Aluminium foil blisters.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal and other handling**

No special requirements

## **7 MARKETING AUTHORISATION HOLDER**

Goldshield Pharmaceuticals Limited  
NLA Tower  
12-16 Addiscombe Road  
Croydon  
Surrey  
CRO OXT  
United Kingdom

## **8 MARKETING AUTHORISATION NUMBER**

PA 899/14/1

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

Date of first authorisation: 14 October 1994

Date of last renewal: 14 October 2009

## **10 DATE OF REVISION OF THE TEXT**

June 2011