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

MacroBID 100mg Prolonged-Release Capsules is indicated for the treatment of and prophylaxis against acute or recurrent, uncomplicated lower urinary tract infections; either spontaneous or following surgical procedures caused by micro-organisms sensitive to nitrofurantoin (see Section 5.1). MacroBID 100mg Prolonged-Release Capsules is indicated in adults, children over 12 years.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

* Dosage adjustments may be necessary for patients including the elderly with significant renal impairment (see section 4.4)
** See precautions and warnings (section 4.4) for risks associated with long-term therapy

Indication	Age group	Dose regimen	Duration
Acute or Recurrent Uncomplicated lower UTI	Adults (18-64 years) & Children over 12 years of age	100 mg twice daily	7 days
	Elderly (65 years and over)*		
Surgical Prophylaxis	Adults (18-64 years) & Children over 12 years of age	100 mg twice daily	On the day of procedure and three days thereafter
	Elderly (65 years and over)*		
Long term suppressive therapy	Adults (18-64 years) & Children over 12 years of age	100 mg twice daily	Bedtime is suggested
	Elderly (65 years and over)*		

Renal impairment
Patient with renal impairment will require renal function monitoring during treatment with nitrofurantoin, Dosage adjustments may be necessary in patients including the elderly with mild to moderate renal impairment (see section 4.3, 4.4 and 4.8).

Nitrofurantoin may be used with caution as short-course therapy only for the treatment of lower urinary tract infection in individual cases with an eGFR between 30-44 ml/min to treat resistant pathogens, when the benefits are expected to outweigh the risks.

Hepatic impairment
Nitrofurantoin should be used with caution in patients with hepatic impairment especially elderly. patients on long term nitrofurantoin therapy may require monitoring (see section 4.4).

Paediatric population (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 12years old, consideration should be given to the use of Furadantin Suspension.

Method of administration
For oral use. The dose should be taken with food or milk (e.g. at meal times)

4.3 Contraindications

● Hypersensitivity to the active substance, other nitrofurans or to any of the excipients listed in section 6.1.

● Patients suffering from renal dysfunction with an eGFR below 45 ml/minute.

● G6PD deficiency: May produce neonatal haemolysis if used at term. Only small amounts are present in breastmilk 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 haemolyticanaemia in the foetus or in the newborn infant due to immature erythrocyteenzyme systems.

4.4 Special warnings and precautions for use

Nitrofurantoin is not effective for the treatment of renal parenchymal infections such as pyelitis or pyelonephritis as well as associated renal cortical or perinephric abscesses. 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 renal impairment, pulmonary disease, hepatic dysfunction, neurological disorders, and allergic diathesis.

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

Neuropathy
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 (paraesthesia).

Patients with renal impairment
Nitrofurantion should be used with caution in patients with renal impairment see sections 4.2 and 4.3, Patients with mild to moderate renal dysfunction will require adequate monitoring, as they may experience an increase in pulmonary adverse events when taking Nitrofurantoin, see section 4.2, and 4.8.
Nitrofurantoin is not recommended for use in patients with severe renal impairment see section 4.3

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

Acute pulmonary reactions occur within the first week of treatment and are reversible. 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 xray, and eosinophilia. In subacute pulmonary reactions, fever and eosinophilia occur less often than in the acute form (see section 4.8).

Chronic pulmonary reactions occur rarely in patients who have received continuous therapy for six months or longer and are more common in elderly patients.

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).

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. Lupus-like syndrome associated with pulmonary reactions to nitrofurantoin has been reported (see section 4.8).

Hematologic Effects
Nitofurantoin 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. Agranulocytosis, leucopenia, granulocytopenia, haemolytic anaemia, thrombocytopenia, glucose-6-phosphatedehydrogenase deficiency anaemia, megaloblasticanaemia and eosinophilia have occurred. Aplastic anaemia has been reported rarely. Cessation of therapy has generally returned the blood picture to normal.

Clostridium difficile associated diarrhea (CDAD)
Gastrointestinal reactions may be minimised by taking the drug with food or milk or by adjustment of dosage. Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including nitrofurantoin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.

Hepatotoxicity
Hepatic reactions including hepatitis, autoimmune 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. 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. If hepatitis occurs, the drug should be withdrawn immediately and appropriate measures should be taken. Rarely liver failure (which maybe fatal) have been reported after nitrofurantoin usage. Drug induced autoimmune hepatitis is also noted with not known frequency.

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.

Carcinogenicity
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.

Antimicrobial agents
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 occurs elsewhere in the body.

Laboratory Tests
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).

Excipients
Lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Sucrose: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Sodium: This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of magnesium trisilicate reduces absorption of nitrofurantoin.
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 antibacterial it will have the following resulting interactions:
Typhoid Vaccine (oral):Antibacterials inactivate oral typhoid vaccine.

4.6 Fertility, pregnancy and lactation

Pregnancy

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.
Based on clinical experience in humans over many years, there is no evidence of any teratogenic effects of nitrofurantoin on the foetus. Study in rats has shown reproductive toxity (see section 5.3)

Breast-feeding

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.

Fertility
No data available

4.7 Effects on ability to drive and use machines

Macrobid has major influence on the ability to drive and use machines. It 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

A tabulated list of undesirable effects is outlined below:
The undesirable effects are listed according to organ systems and following frequencies:
Rare (1/10,000 to <1/1,000)
Not known (cannot be estimated from the available data)

System organ class	Frequency	Adverse reaction
Infections and infestations	Not known	Superinfections by fungi or resistant organisms such as Pseudomonas. However, these are limited to the genitourinary tract.
Blood and lymphatic system disorders	**Rare** Not known	**Aplastic anaemia** Agranulocytosis,

		leucopenia, granulocytopenia, haemolyticanaemia, thrombocytopenia, glucose¬6-phosphatedehydrogenase deficiency anaemia, megaloblasticanaemia and eosinophilia
Immune system disorders	**Not known**	Anaphylaxis, angioneuroticoedema, cutaneous vasculitis and allergic skin reactions
Psychiatric disorders	Not known	Psychotic reactions depression, euphoria, confusion
Nervous system disorders	Not known	Benign intracranial hypertension Peripheral neuropathy including optic neuritis (sensory as well as motor involvement), nystagmus, vertigo, dizziness, headache and drowsiness.
Cardiac disorders	Rare	Collapse and cyanosis
Respiratory, thoracic and mediastinal disorders	Not known	Permanent impairment of pulmonary function, Pulmonary fibrosis; possible association with lupus-erythematous-like syndrome. Acute pulmonary reactions, Subacute pulmonary reactions* Chronic pulmonary reactions Bronchiolitis obliterans organising pneumonia. Dyspnoea, cough
Gastrointestinal disorders	Not known	Sialoadenitis, pancreatitis, anorexia, emesis, abdominal pain, diarrhea and nausea.
Hepatobiliary disorders	**Rare** Not known	**Liver failure (which maybe fatal)** Chronic active hepatitis (fatalities have been reported), hepatic necrosis, autoimmune hepatitis, cholestatic jaundice,
Skin and subcutaneous tissue disorders	Not known	Drug Rash With Eosinophilia And Systemic Symptoms (DRESS syndrome). Lupus-like syndrome associated with pulmonary reaction. Exfoliative dermatitis and erythema multiforme (including Stevens-Johnson Syndrome), maculopapular, erythematous or eczematous eruptions, urticaria, rash, and pruritus. Transient alopecia
Renal and urinary disorders	Not known	Interstitial nephritis Yellow or brown discolouration of urine
Congenital, familial and genetic disorders	Not known	Acute porphyria
General disorders and administration site conditions	Not known	Asthenia, fever, chills, drug fever and arthralgia
Investigations	Not known	False positive urinary glucose

*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. 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Symptoms
Symptoms and signs of overdosage include gastric irritation, nausea and vomiting.

Management
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

ATC classification
Pharmacotherapeutic group: Antibacterial
ATC Code: J01XE01

Mechanism of action
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.

Resistance
Transferable resistance to nitrofurantoin is a rare phenomenon. There is no cross resistance to antibiotics and sulphonamides.

Susceptibility testing interpretive criteria
Susceptibility testing breakpoints MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for nitrofurantoin and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

Efficacy against specific pathogens
Nitrofurantoin is specifically indicated for the treatment of infections 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.

5.2 Pharmacokinetic properties

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

Biotransformation

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.

Elimination

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

The available genotoxicity data indicate that nitrofurantoin is a mutagen. Two-year carcinogenicity studies in rats and mice reported carcinogenic effects. The relevance of the genotoxic and carcinogenic potential of nitrofurantoin to human is unknown. Extensive clinical use of nitrofurantoin over 65 years has not found any conclusive evidence for carcinogenic effects at therapeutic dosages.
In rats, at high doses a temporary halt in spermatogenesis was observed in male and ovarian degeneration and atrophy occurred in female.
No decreased fertility was observed in animal studies.
In rats, the administration of nitrofurantoin during gestation has been shown to be toxic to the embryo, including decreased growth.

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)
Ammonium Hydroxide (E527)
Simethicone

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

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8 MARKETING AUTHORISATION NUMBER

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