SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nitrofurantoin Bristol Laboratories 50mg Capsules, Hard
Nitrofurantoin Bristol Laboratories 100 mg Capsules, Hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg of Nitrofurantoin anhydrous in macrocrystalline form.
Excipients with known effect: Also contains 68.63 mg of lactose monohydrate.

Each capsule contains 100 mg of Nitrofurantoin anhydrous in macrocrystalline form.
Excipients with known effect: Also contains 137.26 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard

Yellow/White hard gelatin capsules of size “4” and imprinted with ‘BL’ on cap and ‘50’ on body, containing light yellow crystalline powder. The dimensions of the capsules are 14.3 ± 0.3mm.

Capsule, hard

Yellow/Yellow hard gelatin capsules of size “2” and imprinted with ‘BL’ on cap and ‘100’ on body, containing light yellow crystalline powder. The dimensions of the capsules are 17.6 ± 0.3 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nitrofurantoin is indicated for the treatment of and prophylaxis against acute or recurrent, uncomplicated lower urinary tract infections or pyelitis either spontaneous or following surgical procedures when due to susceptible micro-organisms (see section 4.4 and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Adults
Acute Uncomplicated Urinary Tract Infections (UTIs): 50 mg four times daily for seven days.

Severe chronic recurrence (UTIs): 100 mg four times daily for seven days.

Long term suppression: 50-100 mg once a day.

Prophylaxis: 50 mg four times daily for the duration of procedure and for three days thereafter.

Paediatric population
Children and Infants over three months of age
Acute Urinary Tract Infections: 3mg/kg day in four divided doses for seven days.

Suppressive - 1mg/kg, once a day.

For children under 25 kg body weight consideration should be given to the use of Nitrofurantoin Suspension.

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 (see section 4.8).

Renal impairment
Nitrofurantoin is contraindicated in patients with renal dysfunction and in patients with an eGFR of less than 45 ml/minute (see sections 4.3 & 4.4).

Method of administration
For oral use

This medicine should always be taken with food or milk. Taking Nitrofurantoin with a meal improves absorption and is important for optimal efficacy.

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 of less than 45 ml/minute. Nitrofurantoin may be used with caution as short-course therapy only for the treatment of uncomplicated 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.
- 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 unilaterally non-functioning kidney. A surgical cause for infection should be excluded in recurrent or severe cases.

Nitrofurantoin may be used with caution as short-course therapy only for the treatment of uncomplicated 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.

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 (paraesthesia).

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

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. If hepatitis occurs, the drug should be withdrawn immediately, and appropriate measures should be taken.

Pulmonary adverse reactions
Acute, subacute and chronic pulmonary reactions have been observed in patients treated with nitrofurantoin. If these reactions occur, nitrofurantoin should be discontinued immediately. Signs of pulmonary damage include difficulty and or pain when breathing, shortness of breath and coughing up blood or mucus.

Chronic pulmonary reactions
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).

Acute pulmonary reactions
Pulmonary reactions may be acute and usually occur within the first week of treatment. Increased vigilance for respiratory symptoms in patients who have just started therapy is warranted (especially in the elderly).

Patient 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 sign of haemolysis in those with suspected glucose-6-phosphate dehydrogenase deficiency.

For long-term treatment, monitor patients closely for evidence of hepatitis or pulmonary symptoms or other evidence of toxicity.

Discontinue treatment with Nitrofurantoin if otherwise unexplained pulmonary, hepatic, haematological or neurological syndromes occur.

Important information regarding the ingredients of this medicine

This medicinal product contains Lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products 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
5. alkalisation.
6. Anti-bacterial antagonism by quinolone anti-infectives.
7. Interference with some tests for glucose in urine.
8. As Nitrofurantoin belongs to the group of Anti-bacterials, it will have the following interactions:
    - Typhoid Vaccine (oral): Antibacterials inactivate oral typhoid vaccine.

4.6 Fertility, pregnancy and lactation

Pregnancy

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
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

Nitrofurantoin may cause dizziness and drowsiness and the patient should not drive or operate machinery if affected this way.

4.8 Undesirable effects

Undesirable effects reported for nitrofurantoin are listed below according to system organ class.
Very common (> 1/10)
Common (> 1/100, < 1/10)
Uncommon (≥ 1/1000, < 1/100)
Rare (≥ 1/10,000, < 1/1000)
Very rare (< 1/10,000), not known (cannot be estimated from the available data)

MedDRA organ class	**Very common**	**Rare**	**Not known**
Infections and infestations			Superinfections by fungi or resistant organisms such as Pseudomonas. However, these are limited to the genitourinary tract
Blood and lymphatic system disorders		Aplastic anaemia	Agranulocytosis, leucopenia, granulocytopenia, haemolytic anaemia, thrombocytopenia, glucose-6-phosphate dehydrogenase deficiency, anaemia, megaloblastic anaemia

			and eosinophilia
Immune system disorders			Anaphylaxis, angioneurotic oedema and allergic skin reactions
Psychiatric disorders[2]			Depression, euphoria, confusion, psychotic reactions,
Nervous system disorders[2]			Benign intracranial hypertension, peripheral neuropathy including optic neuritis (sensory as well as motor involvement), optic nystagmus, vertigo, dizziness, headache and drowsiness.
Cardiac disorders		Collapse and cyanosis	
Respiratory, thoracic and mediastinal disorders			[s] Pulmonary fibrosis; possible association with lupus erythematous- like syndrome. acute pulmonary reactions*, subacute pulmonary reactions*, chronic pulmonary reactions*, cough, dyspnoea
Gastrointestinal disorders			abdominal pain, diarrhoea, sialadenitis, pancreatitis, anorexia, emesis and nausea
Hepatobiliary disorders			Chronic active hepatitis (fatalities have been reported), hepatic necrosis, autoimmune hepatitis, cholestatic jaundice
Skin and subcutaneous tissue disorders			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, cutaneous vasculitis, urticaria, rash, and pruritus. transient alopecia
Renal and urinary disorders			Interstitial nephritis, yellow or brown discolouration of urine
General disorders and administration site conditions			Asthenia, fever, chills, drug fever and arthralgia.
Investigations			False positive urinary glucose

*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

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

4.9 Overdose

Symptoms:

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

Management:

There is no known specific antidote. However, Nitrofurantoin can be haemodialyzed in cases of recent ingestion. Standard treatment is by induction of emesis or by gastric lavage. Monitoring of full blood count, liver function, and pulmonary function tests

are recommended. A high fluid intake should be maintained to promote urinary excretion of the drug.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Nitrofuran derivatives
ATC Code: J01XE01

Mechanism of action

Nitrofurantoin is a nitrofuran. Therapeutically active concentrations are achieved only in the urine. Nitrofurantoin is most active in acidic urine, and if the pH value is lower than 8 the antibacterial activity is mostly lost. The precise mechanism of action is not known. Several modes of action have been described. Nitrofurantoin inhibits a number of bacterial enzymes. It also inhibits bacterial ribosomal proteins, and hence results in complete inhibition of bacterial protein synthesis.

Nitrofurantoin may also cause damage to the DNA.

Mechanism of resistance
Resistance rarely develops during treatment with nitrofurantoin, possibly because nitrofurantoin has a number of different modes of action. Resistance may, however, occur with long-term treatment. Plasmid-encoded resistance has been reported in *E. coli*. Reduced sensitivity has been observed among ESBL-producing intestinal bacteria. Resistance may be due to a loss of nitrofuran reductases that produce the active intermediate products.

Breakpoints

The following breakpoints have been set by EUCAST:

Staphylococcus saprophyticus (uncomplicated urinary tract infections only)	S ≤ 64, R > 64 mg/L
Enterococcus faecalis (uncomplicated urinary tract infections only)	S ≤ 64, R > 64 mg/L

Streptococcus agalactiae (uncomplicated urinary tract infections only)	S ≤ 64, R > 64 mg/L
Escherichia coli (uncomplicated urinary tract infections only)	S ≤ 64, R > 64 mg/L

Susceptibility

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infection is questionable

Commonly susceptible species

Aerobic gram-positive micro-organisms

Aerobic gram-negative microorganisms

Anaerobic microorganisms

Other microorganisms

Species for which acquired resistance may be a problem

Aerobic gram-positive micro-organisms

Aerobic gram-negative micro-organisms

Inherently resistant organisms

Aerobic gram-positive microorganisms

Aerobic gram-negative microorganisms

Other micro-organisms

5.2 Pharmacokinetic properties

The Nitrofurantoin macro crystals are specially formulated. The controlled crystal size of the active substance nitrofurantoin macrocrystals, alters the speed of absorption to reduce the incidence of nausea without any decrease in antibacterial efficacy. Clinical

and animal studies indicate that Nitrofurantoin macrocrystals therapy decreases the likelihood of nausea in patients who might experience these symptoms on Nitrofurantoin therapy.

Absorption
Orally administered Nitrofurantoin is readily absorbed in the upper gastrointestinal tract at a slower rate and to reduced extent when compared to microcrystalline Nitrofurantoin. Blood concentrations at therapeutic dosage are usually low with an elimination half-life of about 30 minutes or less.

Elimination
Maximum urinary excretion usually occurs 4-5 hours after administration of macrocrystalline Nitrofurantoin. Urinary drug dose recoveries of about 25-30% are obtained.

5.3 Preclinical safety data

Carcinogenic effect of nitrofurantoin in animal studies was observed. However, human data and extensive use of nitrofurantoin over 50 years do not support such observations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PL 17907/0520
Capsule Content
Lactose monohydrate
Maize starch
Purified talc

Capsule Shell
Iron Oxide Yellow (E172)
Titanium dioxide (E171)
Gelatin

Printing ink

Shellac (E904)
Propylene glycol (E1520)
Black iron oxide (E172)

PL 17907/0521
Capsule Content
Lactose monohydrate
Maize starch
Purified talc

Capsule Shell
Iron Oxide Yellow (E172)
Titanium dioxide (E171)
Gelatin

Printing ink
Shellac (E904)
Propylene glycol (E1520)
Black iron oxide (E172)

6.2 Incompatibilities

Not known.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30 ℃

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6.5 Nature and contents of container

White opaque PVC /aluminium blisters of 10, 14, 15, 20, 28, 30 and 100 capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal

7. MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited
Unit 3, Canalside, Northbridge Road,
Berkhamsted, Hertfordshire, HP4 1 EG,
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 17907/0520
PL 17907/0521

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/07/2021

10. DATE OF REVISION OF THE TEXT

02/10/2023