1.3.1.1 Approved Professional Information for` Medicines for Human Use Cleaned amended copy

S NO		REFERENCE
	SCHEDULING STATUS **S4**	
	1. NAME OF THE MEDICINE **[ZOCZEN]** 50 mg, Hard gelatin capsules. **[ZOCZEN]** 100 mg, Hard gelatin capsules.	
	2. QUALITATIVE AND QUANTITATIVE COMPOSITION **[ZOCZEN]** 50 mg : Each capsule contains 50 mg Nitrofurantoin For full list of excipients, see section 6.1. Contains: Sugar free **[ZOCZEN]** 100 mg : Each capsule contains 100 mg Nitrofurantoin For full list of excipients, see section 6.1. Contains: Sugar free	
	3. PHARMACEUTICAL FORM **[ZOCZEN] 50 mg :** Hard gelatin capsules of size ‘4’ with white opaque body imprinted with ‘50’ and yellow opaque cap imprinted with ‘NMC’ with black ink, filled with yellow to light yellow granular powder. **[ZOCZEN] 100 mg :** Hard gelatin capsules of size ‘2’ with yellow opaque body imprinted with ‘100’ and yellow opaque cap imprinted with ‘NMC’ with black ink, filled with yellow to light yellow granular powder.	

	4. CLINICAL PARTICULARS	
	4.1. Therapeutic indications	
	[ZOCZEN] is indicated for the treatment and prevention of recurrence of uncomplicated lower urinary tract infections e.g. pyelonephritis, pyelitis and cystitis. It is not indicated for the treatment of associated renal, cortical or perinephric abscesses.	
	4.2. Posology and method of administration	
	Adults ***Acute urinary tract infections:*** 50 mg to 100 mg four times a day, with meals and at bedtime. ***To prevent recurrences***: 50 mg to 100 mg per day **[ZOCZEN]** may be given with food or milk to further minimise gastric upset. Therapy should be discontinued for at least one week and for at least 3 days after sterility of the urine is obtained. Continued infection indicates need for re-evaluation. Nitrofurantoin is highly soluble in urine, to which it may impart a brown colour.	
	SPECIAL POPULATION **Paediatric patients:** **Acute urinary tract infections:** Should be calculated on the basis of 5 to 7 mg/kg of body mass per 24 hours to be given in divided doses four times a day (contraindicated for children under one month) To prevent recurrences: 1 mg/kg/day for long-term therapy.	
	Method of administration **[ZOCZEN]** is administered orally.	
	4.3. Contraindications	
	[ZOCZEN] is contraindicated:	

	• In patients with known sensitivity to nitrofurantoin microcrystals and any of the excipients of **[ZOCZEN]**. • In patients with a deficiency of glucose 6-phosphate dehydrogenase or nursing mothers of infants with this deficiency. • Anuria, oliguria and renal impairment are contraindications to therapy with **[ZOCZEN]**. Treatment of this type of patient carries an increased risk of toxicity because of impaired excretion of the Nitrofurantoin. • Pregnant women at term, as well as infants under one month of age, because of the possibility of haemolytic anaemia due to immature enzyme systems (glutathione instability). **Acute porphyria** • Patients suffering from renal impairment with an eGFR of less than 45mL/min.	
	4.4. Special warnings and precautions for use	
	• Prolonged use of **[ZOCZEN]** is not recommended. • A course of therapy should not exceed 14 days and repeated courses should be separated by rest periods. • Pseudomonas is the organism most commonly implicated in superinfections in patients treated with **[ZOCZEN].** • Nitrofurantoin is not effective for the treatment of parenchymal infections of unilaterally nonfunctioning 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. • Cases of haemolytic anaemia of the primaquine sensitivity type have been induced by **[ZOCZEN]**. • Acute, subacute and chronic pulmonary reactions have been observed in patients treated with nitrofurantoin. If these reactions occur, nitrofurantoin should be discontinued immediately. • Patients with a history of asthma may experience acute asthmatic attacks. • 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). • 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).	

	• **[ZOCZEN]** is not effective for the treatment of parenchymal infections of unilateral non-functioning kidney. A surgical cause for infection should be excluded in recurrent or sever cases. • The haemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. Any sign of haemolysis is an indication to discontinue the **[ZOCZEN]**. • Gastrointestinal reactions may be minimised by taking the medicine with food or milk, or by adjustment of dosage. • Discontinue treatment with Nitrofurantoin if otherwise unexplained pulmonary, hepatic, haematological or neurological syndromes occur.	
	4.5 Interaction with other medicines and other forms of interaction	
	• Probenecid or sulphinpyrazone may reduce the excretion of nitrofurantoin as in **[ZOCZEN]** and should not be given concomitantly. • Increased absorption with food or medicines delaying gastric emptying. • **[ZOCZEN]** decreased absorption with magnesium trisilicate. • **[ZOCZEN]** decreased anti-bacterial activity by carbonic anhydrase inhibitors and urine alkalisation. • Anti-bacterial antagonism by quinolone anti-infectives. • **[ZOCZEN]** Interference with some tests for glucose in urine. • As Nitrofurantoin as in **[ZOCZEN]** belongs to the group of Antibacterials, it will have the following interactions: • Typhoid Vaccine (oral): Antibacterials inactivate oral typhoid vaccine	

	and certain laboratory tests.	
	4.5. Fertility, pregnancy and lactation **Pregnancy** Data in pregnant women indicate no teratogenicity or fetal/ neonatal toxicity. Animal studies do not show reproductive toxicity as clinically relevant doses. Therefore, **[ZOCZEN]** can be used during pregnancy, except in pregnant women at term, as well as infants under one month of age, because of the possibility of haemolytic anaemia due to immature enzyme systems (glutathione instability).	
	Breastfeeding **[ZOCZEN]** is excreted in breast milk. **[ZOCZEN]** can be used during breastfeeding, but it is contraindicated in those patients with a deficiency of glucose 6-phospahte dehydrogenase or nursing mothers of infants with this deficiency	
	4.6. Effects on ability to drive and use machines Nitrofurantoin can cause dizziness and drowsiness. Patient should be advised not to drive or operate machines until the symptoms disappear.	
	4.7. 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).	

a. **Tabulated list of adverse reactions**

Reported adverse reactions for nitrofurantoin are listed below according to organ systems.

System organ class	Frequency
Infections and infestations	
Superinfections by fungi or resistant organisms such as Pseudomonas. However, these are limited to the genitourinary tract.	Frequency unknown
Blood and Lymphatic system disorders	
Aplastic anemia	Frequent
Agranulocytosis, leucopenia, granulocytopenia, haemolytic anemia, thrombocytopenia, glucose -6-phosphate dehydrogenase deficiency anemia, megaloblastic anemia and eosinophilia.	Frequency unknown
Immune system disorders	
Allergic skin reactions, Angioneurotic oedema and anaphylaxis.	Frequency unknown
Psychiatric disorders	
Depression, euphoria, confusion, psychotic reactions.	Frequency unknown
Nervous system disorders	
Peripheral neuropathy including optic neuritis (sensory as well as motor involvement), nystagmus, vertigo, dizziness, headache and drowsiness. Benign intracranial hypertension.	Frequency unknown
Cardiac disorders	
Collapse and cyanosis.	Frequent
Respiratory, thoracic and mediastinal disorders	

Acute pulmonary reactions, Subacute pulmonary reactions*, Chronic pulmonary reactions, Cough, Dyspnoea, Pulmonary fibrosis; possible association with lupus-erythematous-like syndrome.	Frequency unknown
Gastrointestinal disorders	
Sialadenitis, Pancreatitis, Nausea, Anorexia, Emesis, Abdominal pain and Diarrhoea.	Frequency unknown
Hepatobiliary disorders	
Cholestatic jaundice, Chronic active hepatitis (fatalities have been reported), Hepatic necrosis, autoimmune hepatitis.	Frequency unknown
Skin and subcutaneous tissue disorders	
Transient alopecia Exfoliative dermatitis and erythema multiforme (including Stevens-Johnson Syndrome), maculopapular, erythematous or eczematous eruptions, urticaria, rash, and pruritus. Lupus-like syndrome associated with pulmonary reaction. Medicine Rash With Eosinophilia And Systemic Symptoms (DRESS syndrome), cutaneous vasculitis.	Frequency unknown
Renal and urinary disorders	
Yellow or brown discoloration of urine, interstitial nephritis.	Frequency unknown
General disorders and administration site conditions	
Asthenia, fever, chills, fever and arthralgia.	Frequency unknown
Investigations	
False positive urinary glucose test results	Frequency unknown

	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.	
	f. 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 to SAHPRA via The '6.04 Adverse Drug Reactions Reporting Form'. Found under SAHPRA's publications: https://www/sahpra.org.za/Publications/Index/8	
	4.9 Overdose Symptoms and signs of overdose include gastric irritation, nausea and vomiting. Treatment is symptomatic and supportive.(see section 4.7)	
	5. PHARMACOLOGICAL PROPERTIES	
	5.1. Pharmacodynamic properties	
	A 18.5 Urinary tract antiseptics Pharmacotherapeutic group: antimicrobials for systemic use, Nitrofurantoin derivative.	

	ATC code: J01XE01.	
	Mechanism of action Nitrofurantoin is an antibacterial medicine for specific urinary tract infections. Nitrofurantoin is a broad spectrum antibacterial medicine, active against the majority of urinary pathogens. The wide range of organisms sensitive to the bactericidal activity include: *Escherichia coli* *Enterococcus Faecalis* *Klebsiella Species* *Enterobacter Species* *Staphylococcus Species e.g. S. Aureus, S. Saprophyticus, S. Epidermidis Citrobacter Species* Clinically most common urinary pathogens are sensitive to nitrofurantoin. Most strains of *Proteus* and *Serratia* are resistant. All *Pseudomonas* strains are resistant.	
	5.2. Pharmacokinetic properties	
	The nitrofurantoin macro crystals are specially formulated. The controlled crystal size is designed to control the speed of absorption and thus reduce the incidence of nausea. Clinical and animal studies indicate that Nitrofurantoin therapy decreases the likelihood of nausea in patients who might experience these symptoms on Nitrofurantoin therapy. This special formulation of Nitrofurantoin had not caused any decrease in antibacterial efficacy. **Absorption** Orally administered nitrofurantoin is rapidly and completely absorbed from the gastrointestinal tract and is rapidly excreted in the urine. Blood concentrations at therapeutic dosages are usually low.	

	Elimination Anti-bacterial concentration are not achieved in plasma following ingestion of recommended doses because of rapid elimination, Maximum urinary excretion usually occurs 2-4 hours after administration of nitrofurantoin. Urinary medicine dose recoveries of about 40-45% are obtained. It has an elimination half-life of about 30 minutes.	
	5.3 Preclinical safety data **Not applicable**	
	Environmental Risk Assessment **Not Applicable**	
	6. PHARMACEUTICAL PARTICULARS	
	6.1. List of excipients *Capsules content:* Nitrofurantoin Cellulose microcrystalline (Grade 101) Croscarmellose sodium (Ac-Di-Sol) Magnesium stearate (Ligamed MF-2-V) *Capsules shell:* Iron oxide yellow (E172) Titanium dioxide (E171) Gelatin Purified water *Composition of the ink:* Shellac Dehydrated Alcohol Isopropyl alcohol	

	Butyl alcohol Propylene glycol Strong Ammonia solution Black Iron Oxide Potassium hydroxide Purified water	
	6.2. Incompatibilities Not applicable	
	6.3. Shelf life 24 months	
	6.4. Special precautions for storage	
	The capsules should be stored in light-resistant and preferably, moisture-proof containers. Store at or below 25°C. KEEP OUT OF REACH OF CHILDREN.	
	6.5. Nature and contents of container	
	Blister Pack a) Clear 250 micron PVC - Aluminium foil blister pack: Blister pack comprises of clear thermoformable 250 micron PVC film as the forming film and printed 25 micron Aluminium foil as the lidding material. Pack Sizes: 50's: Printed cardboard carton containing 5 blisters of 10 capsules each. b) White Opaque 250 micron PVC film - Aluminium foil blister pack:	

	Blister pack comprises of white opaque thermoformable rigid 250 micron PVC film as the forming film and printed 25 micron Aluminium foil as the lidding material. Pack Sizes: 50's: Printed cardboard carton containing 5 blisters of 10 capsules each. HDPE Container Pack: For Nitrofurantoin Capsules 50 mg: White opaque round 40 mL HDPE container with 33 mm neck finish closed with white opaque 33 mm – 400 polypropylene continuous thread closure with wad having Tekniplex HS 123 induction sealing liner. Pack size: 50's For Nitrofurantoin Capsules 100 mg: White opaque round 60 mL HDPE container with 33 mm neck finish closed with white opaque 33 mm – 400 polypropylene continuous thread closure with wad having Tekniplex HS 123 induction sealing liner. Pack size: 50's This Nitrofurantoin Capsules 50 mg and 100 mg HDPE bottles shall be further packed in pre-printed carton with a packaging leaflet.	
	6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product No special requirements.	
	7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION AUROGEN SA (Pty) Ltd Woodhill Office Park, Building 1, First Floor	

	53 Phillip Engelbrecht Avenue Meyersdal, Ext. 12, 1448 Johannesburg South Africa	
	8. REGISTRATION NUMBER	
	9. DATE OF FIRST AUTHORISATION	
	10. DATE OF REVISION OF TEXT	

REFERENCES

Ref. no.	Reference name	Pages
Ref 1	South African Innovator, MACRODANTIN 50 mg and 100 mg, Pharmacare Limited. Healthcare park, woodland, Woodmead 2191, South Africa.	**p.2 – 3**
Ref 2	Summary of Product Characteristics, MACRODANTIN 50 mg and 100 mg, - Summary of Product Characteristics (SmPC), Mercury Pharmaceuticals Ltd, Capital House, ing William, Street, London EC4N, 7BL, UK	**p.4– 9**