Approved Professional Information for Medicines for Human Use

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

UNITRO 50, Hard gelatin capsules.

UNITRO 100, Hard gelatin capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

UNITRO 50:

Each capsule contains 50 mg nitrofurantoin. Sugar free.

UNITRO 100:

Each capsule contains 100 mg nitrofurantoin. Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

UNITRO 50:

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.

UNITRO 100:

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

UNITRO 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

UNITRO 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

UNITRO is administered orally.

4.3. Contraindications

UNITRO is contraindicated:

- In patients with known sensitivity to nitrofurantoin microcrystals and any of the excipients of **UNITRO**.
- 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 **UNITRO.**

Treatment of this type of patient carries an increased risk of toxicity because of impaired excretion of 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).
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Acute porphyria

- Patients suffering from renal impairment with an eGFR of less than 45 mL/min.

4.4. Special warnings and precautions for use

Prolonged use of **UNITRO** is not recommended. A course of therapy should not exceed 14 days and repeated courses should be separated by rest periods.

Patients with a history of asthma may experience acute asthmatic attacks.

Elderly patients and patients undergoing prolonged therapy should be monitored for changes in pulmonary function.

Cases of haemolytic anaemia of the primaquine sensitivity type have been induced by **UNITRO**. 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 **UNITRO**.

Pseudomonas is the organism most commonly implicated in super infections in patients treated with **UNITRO**. During **UNITRO** treatments there are lung and liver complications that can be life-threatening (see section 4.8). The treatment should be stopped immediately and the necessary measures should be taken.

Acute, subacute and chronic pulmonary reactions have been observed in patients treated

with **UNITRO**. If these reactions occur, **UNITRO** must be discontinued immediately.

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

Patients with hepatic impairment

Patients should be closely monitored for signs of hepatitis (especially in the long term use). Existing conditions can mask pulmonary and hepatic side effects, there is caution provided when **UNITRO** is used in patients with pulmonary diseases, disturbed hepatic function, neurological disorders and allergic diathesis.

Precautions

Patients should be warned to report early signs of peripheral neuropathy. If peripheral neuropathy occurs the treatment should be discontinued. Care is required in patients with predisposing pulmonary, hepatic, neurological or allergic disorders and in those with conditions (such as anaemia, diabetes mellitus, electrolyte imbalance, debility or vitamin B deficiency) which may predispose to peripheral neuropathy.

Hepatotoxicity

Hepatic reactions, including hepatitis, autoimmune hepatitis, cholestatic jaundice, chronic active hepatitis and hepatic necrosis, can occur. 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, **UNITRO** should be withdrawn immediately and appropriate measures should be taken.

Urine can be coloured yellow or brown after taking **UNITRO**. Patients who taking **UNITRO** can test false positive for urine glucose (if tested for urine reducing substances).

UNITRO 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 severe cases.

4.5 Interaction with other medicines and other forms of interaction

- Probenecid or sulphinpyrazone may reduce the excretion of **UNITRO** and should not be given concomitantly.
- Magnesium trisilicate may reduce the absorption of **UNITRO**.
- **UNITRO** may cause false positive reactions in urine tests for glucose using copper reduction methods.
- Antagonism between nitrofurantoin and nalidixic acid, and nitrofurantoin and oxolinic acid has been demonstrated *in vitro*.
- **UNITRO** should not be given concomitantly with quinolones.

The effect of other medicines on nitrofurantoin:

- Food or medicines that delays gastric emptying increase the bioavailability of **UNITRO**.
- Carbonic anhydrase inhibitors and alkalising medicines can reduce the antibacterial activity of **UNITRO**.
- Magnesium trisilicate, co-administered with **UNITRO**, reduces the absorption of **UNITRO**.
- There may be an antagonism between quinolones and **UNITRO**: simultaneous administration is not recommended.
- Probenecid and sulfinpyrazone can reduce the renal clearance of **UNITRO**.

The effect of nitrofurantoin on other medicines / laboratory tests:

- Typhoid fever vaccine (oral): antibacterial medicines make the oral typhoid fever vaccine ineffective.
- Nitrofurantoin can affect certain laboratory tests. False positive results or incorrect high reading can occur with urinary glucose tests based on the reduction of copper sulphate,

such as Benedict's reagent and Clinitest (Ames). However, there is no interference with the Clinistix test.

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, **UNITRO** 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

UNITRO is excreted in breast milk. **UNITRO** 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

Fertility

In men, at supra-therapeutic doses, a temporary stoppage in spermatogenesis and reduced sperm counts. Clinical doses are not associated with male infertility. No reduced fertility was observed in animal studies. In rats, at high doses observed a temporary stoppage in spermatogenesis.

4.6. Effects on ability to drive and use machines

UNITRO 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:

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.

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

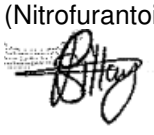
The nitrofurantoin macro crystals are specially formulated. The controlled crystal size is designed to control the speed of absorption and thus reduce the incidence of nausea. Clinical and animal studies indicate that Nitrofurantoin therapy decreases the likelihood of nausea in patients who might experience 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.



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:

UNITRO 50

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

UNITRO 100

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

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

UNITRO 50 55/18.5/207

UNITRO 100 55/18.5/208

9. DATE OF FIRST AUTHORISATION

01 FEBRUARY 2022