PROFESSIONAL INFORMATION FOR
CIPLADANTIN

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CIPLADANTIN 50 capsules

CIPLADANTIN 100 capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CIPLADANTIN 50:

Each capsule contains 50 mg nitrofurantoin in macrocrystalline form, a synthetic chemical of controlled crystal size.

Contains sugar: Lactose monohydrate 81 mg per capsule.

CIPLADANTIN 100:

Each capsule contains 100 mg nitrofurantoin in macrocrystalline form, a synthetic chemical of controlled crystal size.

Contains sugar: Lactose monohydrate 162 mg per capsule.

For a full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Capsules in a macrocrystalline form (a synthetic chemical of controlled crystal size).

CIPLADANTIN 50: yellow coloured free flowing granules filled in hard gelatin capsule with white body printed with “50” in black and yellow cap printed with “NTF” in black.

CIPLADANTIN 100: yellow coloured free flowing granules filled in hard gelatin capsule with white body printed with “100” in black and yellow cap printed with “NTF” in black.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

CIPLADANTIN is indicated for 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

Posology

Therapy should be continued for at least one week and for at least three days after sterility of the urine is obtained. Continued infection indicates need for re-evaluation**.**

CIPLADANTIN is highly soluble in urine, to which it may impart a brown colour.

Adults

- To treat acute urinary tract infections: 50 to 100 mg four times a day, with meals and at bedtime.
- To prevent recurrences: 50 to 100 mg per day.

Special populations

Paediatric population

- To treat acute urinary tract infections: should be calculated on the basis 5 to 7 mg/kg of body mass per 24 hours to be given in divided doses four times a day.
- To prevent recurrences: 1 mg/kg per day for long term therapy.
- CIPLADANTIN must not be given to children less than a month old.

Method of administration

CIPLADANTIN may be taken with food or milk (e.g. at mealtimes) to further minimise gastric upset **(see section 5.2).**

4.3. Contraindications

CIPLADANTIN is contraindicated in the following patients:

- Patients with known hypersensitivity to nitrofurantoin or any of the excipients of CIPLADANTIN listed in section 6.1.
- Anuria, oliguria and renal impairment. Treatment of this type of patients carry an increased risk of toxicity because of impaired excretion of the medicine.
- Pregnant women at term (during labour and delivery).

- Infants under three months of age because of the possibility of haemolytic anaemia due to immature enzyme systems (glutathione instability).
- Patients with a deficiency of glucose 6-phosphate dehydrogenase (G6PD).
- Nursing mothers of infants with a deficiency of glucose 6-phosphate dehydrogenase.
- Acute porphyria.

4.4. Special warnings and precautions for use

CIPLADANTIN 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.

CIPLADANTIN should 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 to 40 mL/min to treat resistant pathogens.

A course of therapy should not exceed 14 days and repeated courses should be separated by rest periods.

Since pre-existing conditions may mask adverse reactions, CIPLADANTIN should be used caution in patients with pulmonary disease, hepatic dysfunction, neurological disorders and allergic diathesis. Treatment must be discontinued if otherwise unexplained pulmonary, hepatic, haematological or neurological reactions occur.

Caution is advised in patients with anaemia, diabetes mellitus, electrolyte imbalance, debilitating conditions and folic acid deficiency.

Patients should be warned to report early signs of peripheral neuropathy. If peripheral neuropathy occurs (paraesthesiae), the treatment should be discontinued.

Acute, subacute or chronic pulmonary reaction has been observed in patients treated with CIPLADANTIN. If these reactions occur, the CIPLADANTIN should be withdrawn and appropriate measures should be taken.

Chronic pulmonary reaction (including pulmonary fibrosis and diffuse interstitial pneumonitis) can develop insidiously and may occur frequently in elderly patients. Close monitoring of the pulmonary conditions of patients receiving long-term therapy is warranted (especially in the elderly).

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

Cases of haemolytic anaemia of the primaquine sensitivity type have been induced by CIPLADANTIN. The haemolysis appears to be linked to a G6PD deficiency in the red blood cells of the affected patients. Any sign of haemolysis is an indication to discontinue the medicine.

CIPLADANTIN should not be given to patients with renal impairment since antibacterial concentrations in the urine may not be attained and toxic concentrations in the plasma can occur.

Although hepatic reactions such as hepatitis, cholestatic jaundice, and hepatic necrosis rarely occur, fatalities have been reported. Patients should be monitored, and treatment be stopped immediately if hepatitis occurs.

CIPLADANTIN may cause false positive reactions in urine tests for glucose using copper reduction methods.

For long-term treatment, patients must be monitored for evidence of toxicity including hepatitis and pulmonary effects.
Gastrointestinal reactions may be minimised by taking CIPLADANTIN with food or milk, or by adjusting the dose.
Pseudomonas is the organism most implicated in superinfections in patients treated with CIPLADANTIN.

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 medicines and other forms of interaction

Probenecid or sulphinpyrazone

Probenecid or sulphinpyrazone may reduce the excretion of nitrofurantoin and should not be given concomitantly.

Magnesium trisilicate

Magnesium trisilicate may reduce the absorption of nitrofurantoin.

Copper reduction methods

Nitrofurantoin may cause false positive reactions in urine tests for glucose using copper reduction methods.

Quinolones

Antagonism between nitrofurantoin and nalidixic acid and nitrofurantoin and oxolinic acid has been demonstrated *in vitro*. Therefore, CIPLADANTIN should not be given concomitantly with quinolines as there is antibacterial antagonism.

Carbonic anhydrase inhibitors (e.g. acetazolamide) and urine alkalinisers (e.g. potassium citrate mixture)

Decreased anti-bacterial activity by carbonic anhydrase inhibitors and urine alkalisation.

Food and medicines delaying gastric emptying (e.g. atropine, hyoscine)

There is an increased absorption with food or medicines delaying gastric emptying.

Oestrogens

In common with other antibiotics, nitrofurantoin may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of oestrogen-containing contraceptive medicines. Therefore, patients should be warned appropriately, and extra contraceptive precautions be taken.

Typhoid vaccine (oral)

CIPLADANTIN belongs to a group of antibacterial medicines that inactivate oral typhoid vaccine.

4.6. Fertility, pregnancy and lactation

Pregnancy

Maternal side effects associated with CIPLADANTIN may adversely affect the course of pregnancy. Therefore, CIPLADANTIN should be used at the lowest possible dose, only after careful assessment.

CIPLADANTIN is contraindicated in weeks 38-42 of pregnancy, during labour and delivery.

Breastfeeding

CIPLADANTIN is contraindicated in infants less than three months old (see **section 4.3**) because of the possible risk of haemolysis of the infants' immature red blood cells. Therefore, nursing mothers should not breastfeed their infants while being treated with CIPLADANTIN.

Fertility

There are no data on fertility in humans.

4.7. Effects on ability to drive and use machines

Patients should be informed that dizziness and drowsiness has been reported during treatment with nitrofurantoin and should not drive or operate machinery if affected.

4.8. Undesirable effects

Infections and infestations:

Frequency not known: superinfections by fungi or resistant organisms such as *Pseudomonas*

Blood and lymphatic system disorders:

Less frequent: aplastic anaemia.

Frequency not known: agranulocytosis, leukopenia, granulocytopenia, haemolytic anaemia, thrombocytopenia and megaloblastic anaemia, G6PD deficiency anaemia, eosinophilia.

Immune system disorders:

Frequency not known: allergic skin reactions, angioedema and anaphylaxis.

Psychiatric disorders

Frequency not known: depression ,euphoria ,confusion ,psychotic reactions.

Nervous system disorders:

Less frequent: peripheral neuropathy including optical neuritis with symptoms of sensory and motor involvement, nystagmus, vertigo, dizziness, headache, drowsiness, benign intercranial hypertension.

Cardiac disorders:

Less frequent: collapse and cyanosis.

Respiratory, thoracic and mediastinal disorders:

Frequency not known: acute pulmonary reactions, subacute pulmonary reactions*, chronic pulmonary reactions, cough, dyspnoea , pulmonary fibrosis; possible association with lupus-erythematous-like syndrome.

Gastrointestinal disorders:

Frequency not known: sialadenitis, anorexia, nausea, vomiting, pancreatitis, emesis, abdominal pain, diarrhoea.

Hepato-biliary disorders:

Frequency not known: cholestatic jaundice, chronic active hepatitis (fatalities have been reported), hepatic necrosis, autoimmune hepatitis.

kin and subcutaneous tissue disorders:

Less frequent: transient alopecia, exfoliative dermatitis, erythema multiforme (including Steven-Johnson syndrome), rash, maculopapular, erythematous or eczematous eruptions, urticaria, pruritus, lupus-like syndrome associated with pulmonary reaction, drug rash with eosinophilia and systemic symptom (DRESS syndrome), cutaneous vasculitis.

Renal and urinary disorders:

Frequency not known: yellow or brown discolouration of the urine.

General disorders and administrative side disorders:

Frequency not known: asthenia, fever, chills, drug fever and arthralgia.

Investigations:

Frequency not known: false positive urinary glucose.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting 359 Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 and to Cipla Medpro (Pty) Ltd. (by e-mail: drugsafetysa@cipla.com) or telephone 080 222 6662 (toll free).

4.9. Overdose

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

There is no known specific antidote. However, nitrofurantoin can be haemodialysed in cases of recent ingestion. Treatment is symptomatic and supportive. Monitoring of full blood count, liver function and pulmonary function tests are recommended. A high fluid intake should be maintained to promote urinary excretion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological class: A 18.5 Urinary tract antiseptics

Pharmacotherapeutic group: Antibacterials for systemic use, nitrofurantoin derivatives.

ATC code: J01XE01.

Nitrofurantoin is an antibacterial medicine for specific urinary tract infections.

Nitrofurantoin exerts bacteriostatic activity against many strains of: *Escherichia coli* and *Enterococci*. (Antibacterial activity is higher in acidic urine.

Many strains of *Enterobacter* species and *Klebsiella* species are resistant to nitrofurantoin. It is not active against most strains of *Proteus* and *Pseudomonas* species.

5.2. Pharmacokinetic properties

Absorption:

Nitrofurantoin microcrystals are specially formulated. The controlled crystal size is designed to control the speed of absorption and thus reduce the incidence of nausea. Orally administered nitrofurantoin is readily absorbed in the upper gastrointestinal tract at a slower rate and to reduce extent when compared to microcrystalline nitrofurantoin. The absorption rate is dependent on crystal size.

Nitrofurantoin is rapidly and completely absorbed from the gastrointestinal tract. Antibacterial concentrations are not achieved in plasma following ingestion of recommended doses because of rapid elimination.

Distribution

On absorption, concentrations in blood and body tissues are low because of rapid elimination, and antibacterial concentrations are not achieved.

Nitrofurantoin crosses the placenta and the blood brain barrier and traces have been detected in breast milk. Degree of protein binding is estimated to be between 60 and 90 %. The plasma half-life is 0.3 to 1 hour.

Metabolism

Nitrofurantoin is metabolised in the liver and most body tissues.

Elimination

About 30 to 40 % of nitrofurantoin is excreted rapidly unchanged into the urine. The average dose of nitrofurantoin yields a concentration in urine of 50 to 200 µg/mL. Maximum urinary excretion usually occurs 4-5 hours after administration of macrocrystalline nitrofurantoin. Urinary medicine dose recoveries of about 25 – 30 % are obtained.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

- Hard gelatin capsule
- Lactose monohydrate
- Maize starch
- Purified talc

The gelatin capsule is composed of:

- Gelatin
- Iron oxide yellow
- Sodium dodecyl sulfate
- Titanium oxide
- Water

Black ink is used for printing on the gelatin capsule is made up of:

- Black iron oxide

- Butyl alcohol
- Dehydrated alcohol
- Isopropyl alcohol
- Potassium hydroxide
- Propylene glycol
- Purified water
- Shellac
- Strong ammonia solution

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

24 months.

6.4. Special precautions for storage

Store at or below 25 °C in the original pack, away from light and moisture.

The blisters should not be removed from the carton until required for use.

6.5. Nature and contents of container

White, opaque NC-coated Alu/PVC blister containing 10 capsules each.

6.6. Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements**.**

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

CIPLADANTIN 50: 53/18.5/0109.107

CIPLADANTIN 100: 53/18.5/0110.108

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 December 2022

10. DATE OF REVISION OF THE TEXT

Not applicable.