PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

CIPROGEN 250 mg (Film-coated tablet)

CIPROGEN 500 mg (Film-coated tablet)

CIPROGEN 750 mg (Film-coated tablet)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CIPROGEN 250 mg film-coated tablet contains ciprofloxacin hydrochloride monohydrate, equivalent to 250 mg ciprofloxacin.

CIPROGEN 500 mg film-coated tablet contains ciprofloxacin hydrochloride monohydrate, equivalent to 500 mg ciprofloxacin.

CIPROGEN 750 mg film-coated tablet contains ciprofloxacin hydrochloride monohydrate, equivalent to 750 mg ciprofloxacin.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

CIPROGEN 250 mg: White, round, biconvex, film-coated tablets with “CF” over score line, “250” on one side and “G” on the other side.

CIPROGEN 500 mg: White, biconvex, capsule shaped, film-coated tablet marked “CF” over score line, “500” on one side and “G” on the other side.

CIPROGEN 750 mg: White, biconvex, capsule shaped, film-coated tablet marked “CF” over score line, “750” on one side and “G” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CIPROGEN tablets are indicated for treatment of the following infections that are caused by bacteria sensitive to ciprofloxacin:

Lower Respiratory Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae* and *Haemophilus parainfluenzae*.

Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis* and *Streptococcus faecalis*.

Skin and Soft Tissue Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Streptococcus pyogenes*.

Gastrointestinal Infections: Infective diarrhoea caused by *Escherichia coli*, *Campylobacter jejuni*, *Shigella flexneri* and *Shigella sonnei*.

Bone Infections: Osteomyelitis due to susceptible Gram-negative organisms.

Gonorrhoea.

Ciprofloxacin is ineffective against *Treponema pallidum*. In the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside must be administered concomitantly.

4.2 Posology and method of administration

CIPROGEN tablets should be swallowed whole with plenty of liquid and may be taken before or after meals.

The dose ranges from 250 - 750 mg twice daily and the duration of treatment depends upon the severity of the infection, clinical response and bacteriological findings. Severe and complicated infections may require prolonged therapy. The usual treatment period for acute infections is 5 – 10 days. Streptococcal infections should be treated for at least 10 days because of the possibility of late complications.

Lower respiratory tract infections:

Mild to moderate: 250 to 500 mg twice daily; severe or complicated: 750 mg twice daily. In cystic fibrosis patients, the dosage is 7,5 to 15 mg/kg body mass/day in two divided doses.

Urinary tract infections:

Acute uncomplicated cystitis and mild to moderate infections: 250 mg twice daily; severe or complicated infections: 500 mg twice daily.

Skin infections:

Mild to moderate infections: 500 mg twice daily; severe or complicated infections: 750 mg twice daily.

Infectious diarrhoea:

500 mg twice daily.

Bone infections:

Mild to moderate infections: 500 mg twice daily; severe or complicated infections:

750 mg twice daily. Treatment may be required for 6 weeks or longer.

Gonorrhoea:

A single dose of 250 mg.

Special populations

Elderly:

Elderly people should receive doses as low as possible depending on the creatinine clearance and severity of the infection.

Dose adjustment for patients with kidney and/or liver insufficiency:

In patients with reduced renal function, the half-life of ciprofloxacin is prolonged, and the dosage needs to be adjusted.

For patients with changing renal function or patients with renal impairment and hepatic insufficiency, monitoring of drug serum levels provides the most reliable basis for dose adjustment.

Dose adjustment of ciprofloxacin for patients with kidney and/or liver insufficiency	
1. Kidney insufficiency:	
1.1 CL_{CR} ≥ 31 ml/min/1,73 m^2 ≤ 60 ml/min/1,73 m^2	Maximum 1000 mg/day orally.
1.2 CL_{CR} ≤ 30 ml/min/1,73 m^2	Maximum 500 mg/day orally.
1.3 Impaired renal function and haemodialysis	As in 1.2 above, on dialysis days, after dialysis.
2. Impaired renal function and CAPD:	
2.1 Oral administration of **CIPROGEN 500 mg** tablet or 2 x 250 mg tablets. 2.2 For CAPD patients with peritonitis, the recommended daily dose is 500 mg 4 times daily.	
3. Liver function disturbances	No dose adjustment.
4. Liver and kidney insufficiency	As in 1.1 and 1.2 above.

Method of administration

Oral use. **CIPROGEN** tablets should be swallowed whole with plenty of liquid and may be taken before or after meals.

4.3 Contraindications

Safety during pregnancy and lactation has not been established.

CIPROGEN is contra-indicated in patients who have shown hypersensitivity to ciprofloxacin or other quinolones.

Concomitant use of fluoroquinolones with ACE inhibitors/Renin-Angiotensin blockers is contraindicated in patients with moderate to severe renal impairment.

4.4 Special warnings and precautions for use

CIPROGEN is contra-indicated in children under 18 years and in growing adolescents, except where the benefit of treatment exceeds the risks. Experimental evidence indicates that species variable reversible lesions of the cartilage of weight-bearing joints have been seen in immature members of certain animal species.

CIPROGEN should be used with caution in patients with a history of convulsive disorders.

CIPROGEN may cause crystalluria and patients receiving **CIPROGEN** should be well hydrated and excessive alkalinity of the urine should be avoided.

Disturbances in blood glucose, including both hyperglycaemia and hypoglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic medicine or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients. (see **section 4.3**). Renal function should be assessed before initiating treatment, and monitored during treatment, with fluoroquinolones of ACE inhibitors/ renin-angiotensin receptor blockers.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN) Stevens Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with **CIPROGEN** (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of these reactions appear, **CIPROGEN** should be discontinued immediately, and an alternative treatment should be considered. If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of **CIPROGEN**, treatment with **CIPROGEN** must not be restarted in this patient at any time.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury (see **section 4.3**)

In a study of volunteers treated with rifampin, moxifloxacin, or both drugs, rifampin reduced the moxifloxacin AUC_{0-24} by 27 % via induction of sulfate conjugation (Weiner et al., 2007). In another study, rifapentine reduced moxifloxacin AUC_{0-24} by 17 % (Dooley et al., 2008). These studies suggest that the most important cause of pharmacokinetic variability for moxifloxacin is concomitantly administered drugs for tuberculosis.

Concurrent administration of **CIPROGEN** with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, the plasma levels of theophylline should be monitored, and dosage adjustments made as appropriate.

CIPROGEN tablets should be administered 1 - 2 hours before, or at least 4 hours after taking iron preparations, antacids containing magnesium, aluminium, calcium, or sucralfate, as interference with absorption may occur. H_2-receptor blockers have no effect on the absorption of ciprofloxacin after oral administration. Administration of fenbufen (a nonsteroidal anti-inflammatory agent) with quinolones may increase the risk of central nervous system stimulation and convulsive seizures.

Transient increases in serum creatinine concentrations may occur in patients receiving cyclosporin concomitantly and monitoring of the serum creatinine is advised.

The action of warfarin may be intensified if administered together with **CIPROGEN**. The action of glibenclamide (hypoglycaemia) may be intensified if administered together with **CIPROGEN**.
Co-administration of probenecid and **CIPROGEN** increases serum concentrations of ciprofloxacin as probenecid interferes with the renal excretion of ciprofloxacin.

Metoclopramide accelerates the absorption of ciprofloxacin, resulting in a shorter time to reach C_{max}. No effect was seen on the bioavailability of ciprofloxacin.

4.6 Fertility, pregnancy and lactation

Safety and/or efficacy has not been established.

4.7 Effects on ability to drive and use machines

Even when taken as prescribed, **CIPROGEN** can affect the speed of reaction to such an extent that the ability to drive or to operate machinery is impaired. This applies particularly in combination with alcohol.

4.8 Undesirable effects

The following side-effects have been reported:

Blood and lymphatic system disorders:

Eosinophilia, leukocytopenia, granulocytopenia, anaemia, thrombocytopenia

Less frequent: leucocytosis, thrombocytosis, haemolytic anaemia, altered prothrombin values.

Metabolism and nutritional disorders:

Less frequent: Hypoglycaemia, particularly in diabetic patients.

Frequency unknown: Hyperglycaemia, hypoglycaemic coma.

Nervous system disorders:

Dizziness, headache, tiredness, nervousness, agitation, trembling, insomnia, peripheral paralgesia, sweating, unsteady gait, convulsions, increase in intracranial pressure, anxiety states, nightmares, confusion, depression, hallucinations, in individual cases psychotic reactions (even progressing to self-endangering behaviour). These reactions may already occur after the first administration of **CIPROGEN**. **CIPROGEN** should be discontinued, and a medical doctor consulted immediately.

Eye, Ear and labyrinth disorders:

Impaired taste and smell, visual disturbances (e.g., diplopia, colour vision), tinnitus, transitory impairment of hearing (high frequencies)

Cardiac disorders:

Tachycardia, hot flushes, migraine, fainting

Gastrointestinal disorders:

Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain, flatulence, anorexia. If severe or persistent diarrhoea occurs during or after treatment, a doctor must be consulted.

This side-effect can hide a serious intestinal disease (pseudomembranous colitis) which may require immediate treatment. Treatment with **CIPROGEN** should be discontinued immediately and appropriate therapy initiated. Medicines that inhibit peristalsis should not be given.

Hypersensitivity reactions:

Rashes, pruritus, drug fever, petechiae, haemorrhagic bullae, vasculitis. Erythema nodosum, erythema exsudativum multiforme, Stevens-Johnson syndrome, Lyell syndrome, interstitial nephritis, hepatitis, hepatic necrosis.

Anaphylactic/anaphylactoid reactions (facial, vascular and laryngeal oedema, dyspnoea progressing to life-threatening shock), in some instances after the first administration. In these cases, **CIPROGEN** has to be discontinued and medical treatment (e.g., treatment for shock) is required.

Skin and subcutaneous tissue disorder

Frequency: Not known – DRESS

Other side-effects:

Joint pain, joint swelling. Less frequently: general feeling of weakness, muscular pains, tendosynovitis, photosensitivity, transient impairment in kidney function including transient kidney failure.

Achillotendinitis: Cases of partial or complete rupture of the Achilles tendon have been reported especially in the elderly on prior systemic treatment with glucocorticoids. At any signs of achillotendinitis (e.g., painful swelling) the administration of **CIPROGEN** should be discontinued and a physician consulted.

Long-term or repeated administration of **CIPROGEN** can lead to superinfections with resistant bacteria or yeast-like fungi.

Care is necessary in patients with impaired hepatic or renal function, glucose –6-phosphate dehydrogenase deficiency or myasthenia gravis. Exposure to strong sunlight or sunlamps should also be avoided.

Influence on laboratory parameters/urinary sediment:

There can be a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, especially in patients with previous liver damage; temporary increase in urea, creatinine or bilirubin in the serum; in individual cases: hyperglycaemia, crystalluria or haematuria.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Acute, excessive overdosage may lead to reversible renal toxicity. Monitoring of renal function is recommended together with routine emergency measures and administration of magnesium and calcium containing antacids to reduce the absorption of ciprofloxacin. Less than 10 % of ciprofloxacin in the serum is removed with haemodialysis or peritoneal dialysis.

Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones

A 20.1.1 Broad and medium spectrum antibiotics

ATC code: J01MA02

Ciprofloxacin is a synthetic 4-quinolone derivative with *in vitro* bactericidal activity against the following Gram-positive and Gram-negative organisms. *In vitro* sensitivity does not necessarily imply *in vivo* efficacy.

Acinetobacter	*Hafnia*	*Salmonella enteritidis*	*Aeromonas*
Klebsiella species	*Serratia marcescens*	*Brucella*	*Listeria*
Shigella flaxneri	*Campylobacter jejuni*	*Moraxella catarrhalis*	*Shigella sonnei*
Citrobacter freundii	*Morganella morganii*	*Staphylococcus aureus*	*Citrobacter species*
Neisseria gonorrhoeae	*Staphylococcus epidermidis*	*Corynebacterium*	*Pasteurella*
Streptococcus species	*E. coli*	*Plesiomonas*	*Streptococcus faecalis*
Edwardsiella	*Proteus mirabilis*	*Streptococcus pyogenes*	*Enterobacter cloacea*
Proteus vulgaris	*Vibrio*	*Enterobacter species*	*Providencia rettgeri*
Viridian's streptococci	*Haemophilus influenzae*	*Providencia stuartii*	*Yersinia*
Haemophilus parainfluenzae	*Pseufomonas aeruginosa*		

Organisms that exhibit varying degrees of *in vitro* sensitivity to ciprofloxacin are as follows:
Alcaligenes, Enterococcus faecalis, Flavobacterium, Gardnerella, Legionella, Mycobacterium fortuitum, Mycobacterium tuberculosis, Mycoplasma hominis, Streptococcus agalactiae, Chlamydia.

The following are usually resistant:

Enterococcus faecium, Ureaplasma urealyticum, Nocardia asteroides. With a few exceptions, anaerobes are moderately sensitive (e.g. *Peptococcus, Peptostreptococcus*) to resistant (e.g. *Bacteroides, Treponema pallidum*).

5.2 Pharmacokinetic properties

Ciprofloxacin plasma levels are dose-related and peak 0,5 – 2 hours after oral dosing. The absolute oral bioavailability is approximately 70 % with no substantial loss by first pass metabolism. Distribution of ciprofloxacin is wide and the volume of distribution high, indicating extensive tissue penetration. Ciprofloxacin is present in the lung, skin, fat, muscle, cartilage and bone. It is also present in the active form in the saliva, nasal and bronchial secretions, cerebrospinal fluid and the aqueous humor. Protein binding is low. 40 % to 50 % is excreted in the urine as unchanged drug. Approximately 15 % of a single dose of ciprofloxacin is eliminated as metabolites. Elimination occurs primarily by the kidneys and mainly during the first 12 hours after dosing. Renal clearance is approximately 300 ml/minute. The elimination half-life of unchanged ciprofloxacin is 3 - 5 hours. The elimination kinetics are linear; after repeated dosing at 12 hourly intervals and once steady state has been reached, no accumulation occurs.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide

Corn starch

Crospovidone

Magnesium stearate

Microcrystalline cellulose PH101

Opadry II white Y-22-7719

Pregelatinized maize starch

6.2 Incompatibilities

There are no known incompatibilities.

6.3 Shelf life

Blister pack: 36 months.

Bottle pack: 24 months.

6.4 Special precautions for storage

Store at or below 25 °C in a dry place and protect from light.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

CIPROGEN 250 mg: PVC/PVDC/aluminium blister strip containing 6 or 10 tablets packed into unit cartons. White opaque HDPP containers containing 10 or 100 tablets.

CIPROGEN 500 mg: PVC/PVDC/aluminium blister strip containing 10 tablets packed into unit cartons. White opaque HDPP containers containing 10 or 100 tablets.

CIPROGEN 750 mg: PVC/PVDC/aluminium blister strip containing 10 tablets packed into unit cartons. White opaque HDPP containers containing 10 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Trinity Pharma (Pty) Ltd.

106 16th Road, Building 2

Midrand

1686

8 REGISTRATION NUMBER(S)

CIPROGEN 250 mg: 36/20.1.1/0428

CIPROGEN 500 mg: 36/20.1.1/0429

CIPROGEN 750 mg: 36/20.1.1/0427

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 June 2002

10 DATE OF REVISION OF THE TEXT

9 May 2023