1.5.5.2 Annotated Patient Information Leaflet - clean

SCHEDULING STATUS

S6

CIPROGEN IV, 2mg/ml, solution for infusion

Ciprofloxacin

Read all of this leaflet carefully before you are given CIPROGEN IV

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other healthcare provider.

What is in this leaflet

1. What CIPROGEN IV is and what it is used for.
2. What you need to know before you are given CIPROGEN IV.
3. How to receive CIPROGEN IV.
4. Possible side effects.
5. How to store CIPROGEN IV.
6. Contents of the pack and other information.

1. What CIPROGEN IV is and what it is used for

What CIPROGEN IV is:

CIPROGEN IV contains ciprofloxacin as the active ingredient. It belongs to a group of antibiotics called fluoroquinolones.

What it is used for:

1.5.5.2 Annotated Patient Information Leaflet - clean

- CIPROGEN IV is used in adults to treat severe and/or complicated bacterial infection of the lungs, bladder, gut (diarrhoea), bone, or skin and soft tissues where other antimicrobials used for similar infections were considered not to be an appropriate treatment option, have failed, cannot be used or are not tolerated.
- It is also used to prevent you from getting an infection caused by a bacterium called *Neisseria meningitidis*.

2. What you need to know before you are given CIPROGEN IV

CIPROGEN IV should not be administered to you:

- if you are hypersensitive (allergic) to ciprofloxacin, or any other quinolone antibiotic, or any of the other ingredients of CIPROGEN IV (listed in section 6)**.** Also tell your doctor and pharmacist if you are allergic to any other substances, such as foods, preservatives or dyes;
- if you are pregnant or breastfeeding - Do not use CIPROGEN IV if you are pregnant or breastfeeding;
- if you have previously experienced side effects with the use of quinolone/fluoroquinolone antibiotics relating to your joints, muscles, ligaments, nerves, central nervous system (brain), epilepsy (fits) or mental health (psychiatric disorder) *(see* '*Tell your doctor or healthcare professional before being given the injection if'*);
- if you were born with or have any condition with abnormal heart rhythm whether related to QT time prolongation or not (seen on ECG, electrical recording of the heart) (*see 'Tell your doctor or healthcare professional before being given the injection if'*)

1.5.5.2 Annotated Patient Information Leaflet - clean

- if you are taking other medicines that result in an abnormal heart rate and/or rhythm tracing (ECG) (e.g. prolongation of the "QT time") (*see 'Tell your doctor or healthcare professional before being given the injection if'*);
- if you have an enlargement or "bulge" of a large blood vessel (aortic aneurysm) or a previous episode of aortic dissection (a tear in the aortic wall) or a family history of aortic aneurysm/dissection or other risk factors or existing predisposing conditions (*see 'Tell your doctor or healthcare professional before being given the injection if'*);
- if you have myasthenia gravis (abnormal muscle fatigue leading to weakness and, in serious cases, paralysis) (*see 'Tell your doctor or healthcare professional before being given the injection if'*);
- **if you or your child are younger than 18 years;**
- if you are on treatment for high blood pressure with medicines called ACE inhibitors/renin-angiotensin receptor blockers. Ask your doctor if you are unsure;
- use of fluoroquinolones as contained in CIPROGEN IV is contraindicated in patients with confirmed mitral valve and / aortic valve regurgitation unless no safer appropriate alternative antibiotic is available, has failed or is not well tolerated;
- if you have an infection due to staphylococcal bacteria or infections involving anaerobic bacteria;
- if you are taking a medicine called tizanidine used to help relax certain muscles in your body;
- if you are taking a medicine called agomelatine used to treat depression.

Tell your doctor or healthcare professional before being given the injection if:

- you are currently taking other medicines that can reduce your blood potassium levels;

1.5.5.2 Annotated Patient Information Leaflet - clean

- you have a family history of an enlargement or “bulge” of a large blood vessel (aortic aneurysm) or a previous episode of aortic dissection (a tear in the aortic wall) or other risk factors or existing predisposing conditions (e.g. connective tissue disorders such as Marfan syndrome, Turner syndrome, Vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet’s disease, high blood pressure or known atherosclerosis) (*see ‘You should not be administered CIPROGEN IV’*);
- Sjögren's syndrome (an immune system disorder characterised by dry eyes and dry mouth);
- you have a history of convulsive (fits) disorders (*see ‘You should not be administered CIPROGEN IV’*);
- you are diabetic, as disturbances in blood sugar, including both high blood sugar (hyperglycaemia), and low blood sugar (hypoglycaemia), have been reported usually in diabetic patients receiving treatment at the same time with an oral medicine to lower your blood sugar, or with insulin. Cases of hypoglycaemic coma have been reported. If you are a diabetic patient, careful monitoring of your blood sugar is recommended;
- you have a disorder that can result in prolongation of the QT interval of the heart or if you are taking other medicines that result in an abnormal heart rate and/or rhythm tracing (ECG) (e.g. prolongation of the QT time) (*see’ You should not be administered CIPROGEN IV’*);
- you suffer from myasthenia gravis (*see ‘You should not be administered CIPROGEN IV’*);

1.5.5.2 Annotated Patient Information Leaflet - clean

- you have a history of tendinitis and tendon rupture, especially associated with previous use quinolones or fluoroquinolones, as you should not be given CIPROGEN IV *(see 'You should not be administered CIPROGEN IV'.*

Warnings and precautions

Take special care with CIPROGEN IV:

- CIPROGEN IV may interfere with the interpretation of diagnostic culture tests for tuberculosis.
- CIPROGEN IV may cause your urine to form crystals, you should be well hydrated, and your urine should not be excessively alkaline.
- you should be aware that CIPROGEN IV may cause psychiatric side effects such as anxiety, nightmares, confusion, depression, hallucinations (where you hear, see, smell, taste or feel things that appear to be real but only exist in your mind) and severe psychotic reactions (disturbed, confused, and disrupted patterns of thought) which can lead to self-endangering behaviour. These reactions may occur after the first administration of CIPROGEN IV (*see 'You should not be administered CIPROGEN IV')*.
- There is some evidence, although inconclusive, of a possible association between oral fluoroquinolone use and mitral valve and/or aortic valve regurgitation. A thorough cardiovascular examination including an echocardiogram, should be performed before oral fluoroquinolones are prescribed. Fluoroquinolones should not be prescribed to patients with mitral valve and or aortic valve regurgitation.
- Long term or repeated administration of CIPROGEN IV can lead to superinfections with resistant bacteria or fungi. If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection

1.5.5.2 Annotated Patient Information Leaflet - clean

symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately.

- CIPROGEN IV can cause antibiotic-associated colitis and pseudomembranous colitis (Inflammation of the colon caused by the bacteria *Clostridium difficile* and diarrhoea*).*
- If you suffer from kidney problems.
- CIPROGEN IV may cause liver damage. If you notice any symptoms such as loss of appetite, jaundice (yellowing of the skin), dark urine, itching, or tenderness of the stomach, contact your doctor immediately.
- Your skin becomes more sensitive to sunlight or ultraviolet (UV) light when receiving CIPROGEN IV. Avoid exposure to strong sunlight, or artificial UV light such as sunbeds.
- You may experience symptoms of nerve damage (neuropathy) such as pain, burning, tingling, numbness and/or weakness especially in the feet and legs or hands and arms.
- If you had or are having a solid organ transplant.
- CIPROGEN IV may cause a reduction in the number of white blood cells and your resistance to infection may be decreased. If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately.
- **Severe cutaneous adverse reactions:**

o 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 IV (*see section 4*).

1.5.5.2 Annotated Patient Information Leaflet - clean

- 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 IV 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 IV, treatment with CIPROGEN IV must not be restarted in this patient at any time.

Children/ and adolescents

Do not give CIPROGEN IV to children under the age of 18 years.

Other medicines and CIPROGEN IV

Always tell your healthcare provider if you are taking any other medicine (this includes complementary or traditional medicines).

Tell your doctor if you are taking any of the following medicines:

- It may cause acute kidney injury if you are on treatment with ACE inhibitors/renin-angiotensin receptor blockers used to control your blood pressure and use fluoroquinolones at the same time. Ask your doctor if you are not sure.
- Using CIPROGEN IV at the same time as theophylline (a medicine used to treat asthma), may lead to higher levels of theophylline in the plasma and it prolongs its half-life which causes an increased risk of toxicity. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored, and dosage adjustments made as appropriate.

1.5.5.2 Annotated Patient Information Leaflet - clean

- Simultaneous use of the anti-inflammatory medicine, fenbufen, with quinolones may increase the risk of central nervous system stimulation and seizures (fits).
- If you are receiving ciclosporin (for skin conditions, rheumatoid arthritis and in organ transplantation) while receiving CIPROGEN IV, your serum creatinine concentrations should be monitored as temporary increases in these concentrations have been seen.
- If you are on warfarin (a medicine used to stop the clotting of blood) and receiving CIPROGEN IV, it may lead to warfarin toxicity. Your INR should be closely monitored.
- Simultaneous administration of glibenclamide and CIPROGEN IV can increase the effect of the glibenclamide and lead to low blood sugar (hypoglycaemia).
- Using CIPROGEN IV and probenecid (a medicine used for gout) together increases the concentration of CIPROGEN IV in the blood.
- Metoclopramide (a medicine used for nausea and vomiting) speeds up the absorption of CIPROGEN IV, which causes a shorter time to reach the maximum concentration in the blood.
- Using medicines treating tuberculosis such as rifampicin, rifapentine, with fluoroquinolones, reduces the concentration of the fluoroquinolone in your body.
- Use of CIPROGEN IV with medicines that leads to prolongation of the QT interval of your heart e.g. class IA or III antidysrhythmics (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide), tricyclic antidepressants (e.g. amitriptyline), macrolides (antibiotics e.g. clarithromycin, roxithromycin, azithromycin and erythromycin), antipsychotics (medicines used to treat certain mental and emotional conditions) is contraindicated.
- Methotrexate (for certain types of cancer, psoriasis, rheumatoid arthritis).
- Tizanidine (for muscle spasticity in multiple sclerosis).

1.5.5.2 Annotated Patient Information Leaflet - clean

- Olanzapine (an antipsychotic).
- Clozapine (an antipsychotic).
- Ropinirole (for Parkinson's disease).
- Phenytoin (for epilepsy).
- Zolpidem (for sleep disorders).
- Pentoxifylline (for circulatory disorders).
- Caffeine found in coffee, cola and some medications.
- Duloxetine (for depression, diabetic nerve damage or incontinence).
- Lidocaine (for heart conditions or anaesthetic use).
- Sildenafil (e.g. for erectile dysfunction).
- Agomelatine (for depression).
- Tacrolimus (an immunosuppressive medicine after organ transplant).

Pregnancy and breastfeeding and fertility

You should not receive CIPROGEN IV if you are pregnant or breastfeeding your baby.

If you are pregnant or breastfeeding your baby, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other healthcare provider for advice before given CIPROGEN IV.

Driving and using machinery

It is not always possible to predict to what extent CIPROGEN IV may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which CIPROGEN IV affects them. Your ability to drive a motor vehicle or operate machinery may be impaired by CIPROGEN IV. This applies particularly in combination with alcohol.

1.5.5.2 Annotated Patient Information Leaflet - clean

3. How to receive CIPROGEN IV

- Do not share medicines prescribed for you with any other person.
- Your doctor will tell you how long your treatment with CIPROGEN IV will last.
- If you have the impression that the effect of CIPROGEN IV is too strong or too weak, tell your doctor or pharmacist.
- You will not be expected to give yourself CIPROGEN IV. It will be given to you by a person who is qualified to do so.
- The dosage is determined by the severity and type of infection, the sensitivity of the causative organism. The mass, age and renal function of the patient also determines the dose.
- The duration depends on the type and severity of your infection, the status of your immune system and how your body responds. Your doctor will use the lowest dose that is effective for the shortest time to contain and remove the infection.

The usual dose is:

- The usual dose is 100 mg to 200 mg IV (Intravenous) every 12 hours.
- For complicated and/or severe infections 400 mg may be administered every 12 hours.
- When oral therapy can be substituted, IV therapy can be discontinued.
- The normal duration of IV therapy is 7 days.

Cystic fibrosis:

- For patients with cystic fibrosis the normal dose is 200 mg IV twice daily.
- The low body mass of these patients must be taken into account when determining the dose, (5-10 mg/kg/day).

1.5.5.2 Annotated Patient Information Leaflet - clean

Direction for intravenous administration:

- CIPROGEN IV intravenous infusion may be given over a period of 60 minutes.
- Patient discomfort and the risk of venous irritation may be reduced by slow infusion into a large vein.
- The infusion may be infused directly or after mixing with compatible infusion solutions.
- **THIS PREPARATION MUST BE DILUTED BEFORE USE.**

CIPROGEN IV is compatible with the following infusion liquids at room temperature;

- 0,9 % sodium chloride solution
- Ringer's Solution
- Lactated Ringer's solution
- Sterile water for injections
- 5 % and 10 % dextrose solutions,
- 5 % dextrose with 0,225 % or 0,45 % sodium chloride solutions

These solutions must be administered shortly after admixture.

Important incompatibilities:

Unless compatibility has been confirmed, CIPROGEN IV must be administered separately.

Visual signs of incompatibility are:

- precipitation
- clouding
- discolouration

1.5.5.2 Annotated Patient Information Leaflet - clean

Incompatibility appears with all infusion solutions and medicines that are chemically or physically unstable at the solutions pH (e.g. heparin solutions, penicillins), especially in combination with solutions adjusted to an alkaline pH (ciprofloxacin pH is 3,9 – 4,5).
Any remaining solution must be discarded.

Impaired Renal or Liver Function:

- 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 medicine serum levels provides the most reliable basis for dose adjustment.

Dose adjustment of ciprofloxacin for patients with renal or hepatic impairment	
1. Kidney insufficiency: 1.1 Cl_{Cr} ≥ 31 ml/min/1,73 m^2 1.2 Cl_{Cr} ≤ 30 ml/min/1,73 m^2 1.3 Impaired renal function	 Max 800 mg/day intravenously Max 400 mg/day intravenously As in 1.2 above; after dialysis and haemodialysis on dialysis days.
2. Renal impairment and CAPD (chronic ambulatory peritoneal dialysis): 2.1 Addition of CIPROGEN IV solution to the dialysate (intraperitoneal)	 50 mg ciprofloxacin per litre of dialysate administered 4 times a day
3. Hepatic impairment	No dose adjustment
4. Hepatic and renal impairment	As in 1.1 and 1.2 above

1.5.5.2 Annotated Patient Information Leaflet - clean

If you received more CIPROGEN IV than you should

Since a healthcare professional will administer CIPROGEN IV, he/she will control the dosage. However, in the event of overdosage your doctor will manage the overdosage.

If you missed a dose of CIPROGEN IV

Do not receive a double dose to make up for forgotten individual doses.

Since a healthcare provider will administer CIPROGEN IV, it is unlikely that the dose will be missed.

4. Possible side effects

CIPROGEN IV can have side effects.

Not all side effects reported for CIPROGEN IV are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking CIPROGEN IV, please consult your healthcare provider for advice.

If any of the following happens, stop receiving CIPROGEN IV and tell your doctor immediately or go to the casualty department at your nearest hospital:

- Anaphylactic/anaphylactoid reactions which include swelling of the face, lips, tongue, throat and airways (breathing tubes), difficult breathing, blueness of the skin, low blood pressure, heart failure and can result in death, in some instances after the first administration. In these cases, CIPROGEN IV has to be discontinued and medical treatment (e.g. treatment for shock) is required;
- Rashes, blisters, sensation of skin burning, reddish, painful lumps in a part of the fatty layer of the skin and local eruption of the skin caused by an immune reaction have been reported. Stevens-Johnson syndrome, an extremely serious allergic skin

1.5.5.2 Annotated Patient Information Leaflet - clean

reaction with blistering of the skin, mouth and eyes; Lyell's syndrome, a very serious illness with blistering of the skin, tiny spots caused by bleeding under the skin, skin lesions with inflammation of the blood vessels.

- A medicine reaction that causes rash, fever, inflammation of internal organs, hematologic (blood) abnormalities and systemic illness (DRESS Drug Reaction with Eosinophilia and Systemic Symptoms, AGEP Acute Generalised Exanthematous Pustulosis).
- Convulsions (fits).

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to CIPROGEN IV. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

- Joint pain, joint swelling, general feeling of weakness, muscular pains and painful swelling and inflammation of the tendons have been observed.
- In single cases during the administration of ciprofloxacin, achillotendinitis was observed. Cases of partial or complete rupture of the Achilles tendon have been reported predominantly in the elderly on prior systemic treatment with glucocorticoids. Therefore, at any signs of an achillotendinitis (e.g. painful swelling) the administration of CIPROGEN IV should be discontinued and a doctor be consulted.
- Low blood sugar (hypoglycaemia), particularly in diabetic patients,coma caused by low blood sugar.
- High blood sugar (hyperglycaemia).

1.5.5.2 Annotated Patient Information Leaflet - clean

- Difficulty in sleeping, peripheral change in sensitivity to pain, sweating, unsteady gait (difficulty walking), increase in pressure inside the skull, anxiety states, nightmares, confusion, depression, hallucinations, in individual cases psychotic reactions (even progressing to behaviour where endangering oneself).
- Prolonged QTc interval with symptoms such as blackouts or fainting, because the heart has stopped pumping blood properly and the brain is temporarily starved of oxygen – the heart's rhythm returns to normal within a few minutes and the person regains consciousness.
- Cases where blood flows back into your heart (mitral valve and/or aortic valve regurgitation) have been reported with the use of oral fluoroquinolone antibiotics. It is unknown whether the fluoroquinolone antibiotic is the cause or contributing factor or played no role in the reported cases where a diagnosis was made.

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:

The following side effects have been reported less frequently:

- Increased number of a certain type of white blood cells in the blood, abnormal reduction in white blood cell count, decreased number of red blood cells, reduction in blood platelets, abnormal increase in white blood cells in the blood as a result of infection, increased number of platelets in the blood, lack of red blood cells due to destruction of circulating cells, altered prothrombin values.
- Dizziness, headache (migraine), tiredness, nervousness, agitation, trembling.
- Visual disturbances (e.g. diplopia, colour vision).
- Tinnitus, transitory impairment of hearing, especially at high frequencies.
- Tachycardia (fast heartbeat), hot flushes, migraine, fainting.

1.5.5.2 Annotated Patient Information Leaflet - clean

- Nausea, diarrhoea, vomiting, indigestion, abdominal pain.
- Crystals in the urine related to the use of CIPROGEN IV. You should be well hydrated. Transient impairment in kidney function including transient kidney failure, as well as swelling in between the kidney tubules and blood in the urine have been reported.
- Phlebitis or thrombophlebitis (an inflammation that causes a blood clot to form in a vein, usually in your leg), local irritation and pain at the site of injection have been reported with intravenous administration of ciprofloxacin. Intravenous infusion should be administered by slow infusion over a period of 60 minutes. These reactions are more frequent if the infusion time is 30 minutes or less, or if small veins of the hand are used. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contra-indicated unless the reactions recur or worsen.
- There can be temporary elevations of transaminases, alkaline phosphatase or cholestatic jaundice, (especially in patients with liver damage, temporary increase in urea, creatinine or hyperbilirubinaemia).
- Impaired taste and smell.
- Hepatic necrosis, very seldom progressing to hepatic failure, has been reported.
- Sudden severe pain in your chest, abdomen (tummy) or back.
- Pins and needles, unusual sensitivity to stimuli of the senses, decreased skin sensitivity, tremors, giddiness.
- Fungal superinfections.
- Rapid heartbeat (tachycardia).
- Expansion of blood vessels (vasodilation), low blood pressure.
- Inflammation of the wall of the blood vessels (vasculitis).

1.5.5.2 Annotated Patient Information Leaflet - clean

- Pancreatitis (inflammation of the pancreas).
- Loss of appetite.
- General feeling of illness, weakness, fever and sweating.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

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

By reporting side effects, you can help provide more information on the safety of CIPROGEN IV.

5. How to store CIPROGEN IV

- Before opening: Store at or below 25 ºC.
- After opening immediate use is recommended
- Protect from light.
- Store all medicines out of reach of children.
- Any remaining solution must be discarded.
- Return all unused medicine to your pharmacist.
- Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).
- Do not store in a bathroom
- Do not use after the expiry date stated on the label.

1.5.5.2 Annotated Patient Information Leaflet - clean

6. Contents of the pack and other information

What CIPROGEN IV contains:

The active substance is:

Each 100 millilitres of CIPROGEN IV contains 200 mg ciprofloxacin as the active ingredient.

The other ingredients are*:*

Chlorhydric acid 1N; glucose monohydrate; lactic acid (23 % *m/m*)

What CIPROGEN IV looks like and contents of the pack:

What CIPROGEN IV looks like:

A clear, greenish yellow solution, free from foreign materials.

Contents of the pack:

100 ml and 200 ml Transparent PVC bags.

Holder of Certificate of Registration and Manufacturer

Viatris South Africa (Pty) Ltd.

4 Brewery Street,

Isando, Johannesburg,

1609

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1.5.5.2 Annotated Patient Information Leaflet - clean

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Access to the corresponding Professional Information

Can be obtained on the SAHPRA website