1.5.5.1 Annotated Professional Information for medicines for human use - clean

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

CIPROGEN IV (2 mg/ml, solution for infusion)

2 QUALITIVE AND QUANTITIVE COMPOSITION

CIPROGEN IV contains 2 mg of ciprofloxacin per ml

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Clear greenish yellow solution, free from foreign materials.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CIPROGEN IV is indicated for the treatment of severe and/or complicated infections caused by ciprofloxacin sensitive bacteria where other antimicrobials, approved for a similar indication and to which the causative bacteria are sensitive, were considered not to be an appropriate treatment option, have failed, are contraindicated or not tolerated.

CIPROGEN IV is not indicated/approved for the initiation of treatment (first line treatment) of infections described as mild/moderate/acute and uncomplicated, caused by bacteria sensitive to ciprofloxacin, unless treatment with other appropriate antimicrobials, approved for a similar

indication and to which the causative bacteria are sensitive, have failed, are contraindicated or not tolerated.

CIPROGEN IV is indicated for the treatment of the following bacterial infections, where these infections are compliant with the indication context:

- **Severe and/or complicated lower respiratory tract infections caused by:**

  Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa.

- **Severe and/or complicated urinary tract infections caused by:**

  Citrobacter diversus, Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Morganella morganii, Proteus mirabilis, Providencia rettgeri, Pseudomonas aeruginosa, Serratia marcescens, Staphylococcus epidermidis, Streptococcus faecalis.

- **Skin and soft tissue infections caused by:**

  Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes.

- **Severe and/or complicated gastrointestinal infections:**

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

- **Severe and/or complicated bone infections:**

Osteomyelitis due to susceptible Gram-negative organisms.

- **Gonorrhoea:**

  Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to CIPROGEN IV. Therapy with CIPROGEN IV may be initiated in severe and/or complicated infections before results of these tests are known; once results become available, appropriate therapy should be continued.

4.2 Posology and method of administration

Posology

The dosage of CIPROGEN IV is determined by the severity and type of infection, the sensitivity of the causative organism(s) and the age, mass and renal function of the patient.

The duration of treatment to contain and eradicate infection depends upon the type and severity of the infection, immunological status, clinical response and bacteriological findings. Use the lowest effective dose for the shortest time to contain and eradicate the infection.

In the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside must be administered concomitantly.

Adults:

- The usual dose is 100 mg – 200 mg i.v. every 12 hours.
- For severe and/or complicated infections 400 mg may be administered every 12 hours.

- Intravenous therapy should be discontinued as soon as oral CIPROGEN IV therapy can be substituted.
- The normal duration of intravenous therapy is up to 7 days.
- In cystic fibrosis patients, the normal dose is 200 mg i.v. every 12 hours. The low body mass of these patients should, however, be taken into consideration when determining dosage (5 – 10 mg/kg/day).

Directions of Intravenous Administration:

- CIPROGEN IV should be administered by intravenous infusion over a period of 60 minutes.
- Slow infusion into a large vein will minimise patient discomfort and reduce the risk of venous irritation.
- The infusion solution can be infused either directly or after mixing with the other compatible infusion solutions.
- **THIS PREPARATION MUST BE DILUTED BEFORE USE.**

The aqueous concentrate should be aseptically withdrawn from the CIPROGEN IV ampoule or vial. This should be diluted with a suitable compatible intravenous solution to a final concentration of 1 – 2 mg/ml (see **"**Compatibility and Stability"). The resulting solution should be infused over a period of 60 minutes by direct infusion through a Y-type intravenous infusion set that may already be in place.

Compatibility and Stability:

- CIPROGEN IV is compatible with various intravenous solutions, including sterile water for injections, 0,9 % sodium chloride solution, 5 % and 10 % dextrose solutions, 5 %

dextrose with 0,225 % or 0,45 % sodium chloride solutions, Ringer's solution and Ringer's Lactate solution.

- If CIPROGEN IV has been mixed with one of the above compatible solutions, for microbiological reasons and light sensitivity, these solutions should be administered shortly after admixture.

Important incompatibilities:

- Unless compatibility with other infusion solutions or medicines has been confirmed, they should always be administered separately.
- Signs of incompatibility include precipitation, clouding and discolouration.
- Incompatibility will present with all infusion solutions and medicines that are physically or chemically unstable at the pH of the ciprofloxacin infusion solutions (3,9 – 4,5), e.g. penicillin and heparin solutions, especially in combination with solutions adjusted to an alkaline pH.
- **ANY REMAINING SOLUTION MUST BE DISCARDED.**

Special populations

Impaired Renal or Liver Function:

- In patients with reduced renal function, the half-life of ciprofloxacin may be prolonged.
- The dosage needs to be adjusted as shown below.
- For patients with renal impairment and hepatic insufficiency, monitoring of medicine serum levels provides the most reliable bases 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	Max 800 mg/day intravenously

1.2 Cl_{Cr} ≤ 30 ml/min/1,73 m^2 1.3 Impaired renal function	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

Method of administration

Infusion.

4.3 Contraindications

- CIPROGEN IV is contraindicated in patients with a history of hypersensitivity to ciprofloxacin, any other quinolones, or any of the excipients (*see section 6.1*).
- Pregnancy and lactation.
- Concomitant use of ciprofloxacin with other medicines known to prolong the QT interval, or in patients with disorders that prolong the QT interval to such an extent that it leads to prolonged QTcF interval known to be associated with serious and potentially fatal dysrhythmias or if symptomatic dysrhythmias occur with concomitant use at time intervals shorter than QT intervals usually associated with dysrhythmias *(see section 4.4*).
- A history of tendon, muscle, joint, nerve, central nervous system, epilepsy or psychotic disorders, especially those related to previous quinolone/fluoroquinolone

use where alternative, appropriate antibiotic choices are available for treatment *(see section 4.4*).

- Myasthenia gravis where alternative appropriate antibiotic choices are available to treat these patients *(see section 4.4*).
- Aortic aneurysm and/or dissection or in patients with risk factors or conditions predisposing for aortic aneurysm and/or dissection if alternative appropriate antibiotic choices are available *(see section 4.4*).
- Concomitant use of fluoroquinolones with ACE inhibitors/renin-angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment and in the elderly *(see section 4.4*).
- Psychiatric side effects such as anxiety states, nightmares, confusion, depression, hallucinations, in individual cases psychotic reactions (even progressing to self-endangering behavior) can occur. These reactions may already occur after the first administration of CIPROGEN IV *(see section 4.4*).
- Use of fluoroquinolones 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.
- The combination of CIPROGEN IV and tizanidine is contraindicated because CIPROGEN IV can increase the serum level of tizanidine to such an extent that undesirable effects of tizanidine (hypotension, somnolence, drowsiness, nausea, vomiting, liver dysfunction, miosis, respiratory depression, coma, restlessness) may occur (*see section 4.5*).
- The combination of CIPROGEN IV and agomelatine is contraindicated, as CIPROGEN IV greatly increases the serum level of agomelatine and this may lead to undesirable effects (*see section 4.5*).

Special populations:

Children and adolescents:

- CIPROGEN IV is contraindicated in children less than 18 years.
- In children, arthropathy is reported to occur commonly.

4.4 Special warnings and precautions for use

CIPROGEN IV is contraindicated in children less than 18 years. In children, arthropathy is reported to occur commonly (*see section 4.3* additional information on *Special populations*).

CIPROGEN IV should be used with caution in patients with a history of convulsive disorders. The doctor should quickly be informed of the occurrence and appropriate treatment must be started immediately.

Crystalluria related to the use of CIPROGEN IV has been observed. Patients receiving CIPROGEN IV should be well hydrated and excessive alkalinity of the urine should be avoided (*see sub-header 'Crystalluria')*.

- In the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside must be administered concomitantly (*see section 4.2*).

Dysglycemia:

- 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 (*see section 4.5*).

Severe infections and/or infections due to Gram-positive or anaerobic bacteria:

- CIPROGEN IV should not be used in staphylococcal infections and infections involving anaerobic bacteria.

Gastrointestinal tract:

- Antibiotic-associated colitis and pseudomembranous colitis associated with CIPROGEN IV have been reported (*see section 4.8*).
- These infections can range in severity from mild to potentially fatal.

Hepatobiliary system:

- Hepatocellular necrosis and life-threatening liver failure have been reported with CIPROGEN IV (*see section 4.8)*. Treatment with CIPROGEN IV should be interrupted if signs and symptoms consistent with liver disease such as anorexia, jaundice, dark urine, pruritus or tender abdomen develop.
- Liver function should be checked if there are signs of dysfunction.
- Transient elevated transaminase levels, elevated blood levels for alkaline phosphatase and cholestatic jaundice may occur, particularly in patients with a history of liver dysfunction *(see sub-header 'Influence on laboratory parameters/urinary sediment')*.

Hypersensitivity:

- Anaphylactic/anaphylactoid reactions (e.g. facial, vascular and larynx edema; shortness of breath through to life-threatening shock), in some cases even after the

first intake, have been reported. In these cases, CIPROGEN IV must be discontinued immediately.

Photosensitisation:

- CIPROGEN IV can cause photosensitivity reactions or phototoxic reactions.
- Patients should avoid prolonged exposure to sunlight during therapy with CIPROGEN IV.

Peripheral neuropathy:

- Sensory or sensorimetric polyneuropathy, which may be associated with paraesthesia, hypoaesthesia, dysaesthesia, or weakness, have been reported in patients treated with CIPROGEN IV.

Injection site reactions:

- Intravenous administration should be by slow infusion over 60 minutes *(see section 4.2).*

Cytochrome P450:

- CIPROGEN IV is a moderately potent inhibitor of cytochrome P450 1A2 enzymes. Caution is advised when co-administering medicines that are metabolised by the same enzymes (such as theophylline, methylxanthine, caffeine, duloxetine, clozapine, ropinirole, olanzapine, tizanidine (*see section 4.3 and 4.5)* or agomelatine (*see section 4.3 and 4.5*). Elevated plasma levels and medicine-specific undesirable effects may occur caused by inhibition of the clearance of these medicines (*see section 4.5*).

Aortic aneurysm and aortic dissection, and cardiac valve regurgitation/ insufficiency

- There is some evidence of an increased risk of aortic aneurysm and/or dissection after intake of fluoroquinolones, particularly in the elderly population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Turner syndrome Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, rheumatoid arthritis known atherosclerosis or Sjögren's syndrome).
- In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a doctor in an emergency department of a hospital.
- 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 (*see section 4.3*).

Cardiac disorders:

- CIPROGEN IV has been associated with QT prolongation (*see section 4.3 and 4.8*).
- Concomitant use of CIPROGEN IV with medicines or in patients with disorders that can result in prolongation of the QT interval is contraindicated if concomitant use leads to prolongation of QTc interval associated with serious or potentially fatal dysrhythmias or symptomatic dysrhythmias occur at QTc intervals less than usually

associated with dysrhythmias e.g. class IA or III antidysrhythmic, tricyclic antidepressants, macrolides, antipsychotics *(see section 4.5*) or congenital long QT syndrome, risk of Torsades de Pointes, uncorrected electrolyte imbalance such as hypokalaemia or hypomagnesaemia and cardiac disease such as heart failure, myocardial infarction, or bradycardia.

- A pre-treatment ECG and frequent follow-up ECG monitoring is mandatory with concomitant use to determine whether concomitant use is contraindicated.

- 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 and ACE inhibitors/renin-angiotensin receptor blockers.

Myasthenia gravis:

- The use of CIPROGEN IV in patients with myasthenia gravis is contraindicated if alternative appropriate antibiotic choices are available (*see section 4.3*).
- CIPROGEN IV may exacerbate the symptoms of myasthenia gravis.

Tendinitis and tendon rupture:

- CIPROGEN IV should not be used in patients with a history of tendon disorders, especially those related to previous exposure to quinolone or fluoroquinolone use (*see section 4.3*).

Central nervous system:

Patients with a history of previous central nervous system (CNS) disorders:

- CIPROGEN IV should only be used where alternative appropriate therapies have failed, are contraindicated or not tolerated, since these patients are endangered due to possible central nervous system ~~side~~ undesirable effects.
- Cases of status epilepticus have been reported (*see section 4.3 and 4.8*).

Psychiatric disorders:

- Anxiety states, nightmares, confusion, depression, hallucinations, in individual cases psychotic reactions (even progressing to self-endangering behaviour) can occur. These reactions may already occur after the first administration of CIPROGEN IV (*see section 4.3 and 4.8*).

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; hypoglycaemia *(see section 4.8*).

Crystalluria:

- Since CIPROGEN IV is primarily excreted in the urine and to a lesser extent in the hepatobiliary system, caution is advised in patients with impaired renal function. Crystalluria has been reported and patients should be advised to drink enough fluid.

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 IV (*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 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.

Other warnings and precautions:

- Long term or repeated administration of CIPROGEN IV can lead to superinfections with resistant bacteria or fungi.
- Patients with or a family history of glucose-6-phosphate dehydrogenase deficiency are prone to haemolytic reactions to fluoroquinolones as contained in CIPROGEN IV. Therefore, CIPROGEN IV should be used with caution in these patients.

4.5 Interaction with other medicines and other forms of Interaction

Interactions with active ingredients that are metabolised via cytochrome P450 1A2 isoenzymes:

- CIPROGEN IV is a moderately potent inhibitor of cytochrome P450 1A2 enzymes. Caution should be exercised when co-administering medicines that are metabolised by the same enzymes, such as theophylline, methylxanthine, caffeine, duloxetine, clozapine, ropinirole, olanzapine, tizanidine *(see sections 4.3 and 4.4)* or agomelatine *(see sections 4.3 and 4.4).*

- Concurrent administration of CIPROGEN IV 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 toxicity.** If concomitant use cannot be avoided, plasma levels of theophylline should be monitored, and dosage adjustments made as appropriate.
- Tizanidine must not be co-administered with CIPROGEN IV. The simultaneous administration of CIPROGEN IV and tizanidine led to an increase in tizanidine serum levels. The increase in tizanidine levels was accompanied by an increase in hypotensive and sedative effects such as nausea, vomiting, liver dysfunction, miosis, respiratory depression, coma or restlessness (*see section 4.3 and 4.4)*.
- The concomitant administration of CIPROGEN IV and agomelatine is contraindicated *(see section 4.3 and 4.4*).
- Elevated serum concentrations of caffeine or pentoxifylline (oxypentifylline) have been described with simultaneous administration of CIPROGEN IV.

*Tacrolimus***:**

- Particular caution should be exercised in patients treated concomitantly with tacrolimus and CIPROGEN IV since the known nephrotoxicity or neurotoxicity of both medicines may be exacerbated by concomitant administration.

Non-steroid anti-inflammatory drugs (NSAID):

- Concomitant administration of the nonsteroidal anti-inflammatory medicine fenbufen with quinolones may increase the risk of central nervous system stimulation and seizures.

Ciclosporin:

- Monitoring of serum creatinine concentrations is advised in patients on concomitant ciclosporin therapy, as transient increases in serum creatinine concentrations have been observed.

Vitamin K antagonists:

- The simultaneous administration of CIPROGEN IV and warfarin may lead to warfarin toxicity, therefore, the INR should be closely monitored.

Glibenclamide:

- Concurrent administration of CIPROGEN IV and glibenclamide can potentiate the action of glibenclamide, leading to hypoglycaemia (*see section 4.4*).

Probenecid:

- Probenecid interferes with renal secretion of CIPROGEN IV. Co-administration of probenecid and CIPROGEN IV increases the CIPROGEN IV serum concentrations.

Metoclopramide:

- Metoclopramide accelerates the absorption of CIPROGEN IV, resulting in shorter time to reach maximum plasma concentrations.

ACE inhibitors/renin-angiotensin receptor blockers:

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

Medicines that can prolong the QT interval:

- Concomitant use of CIPROGEN IV with medicines that result in QT prolongation is contraindicated, if concomitant use leads to prolongation of QTc interval associated with serious or potentially fatal dysrhythmias or symptomatic dysrhythmias occur at QTc intervals less than usually associated with dysrhythmias, e.g. class IA or III antidysrhythmics, tricyclic antidepressants, macrolides, antipsychotics (*see section 4.3 and 4.4*).

Lidocaine:

- Ciprofloxacin as contained in CIPROGEN IV reduces the elimination of intravenous lidocaine. An interaction with CIPROGEN IV with corresponding undesirable effects cannot be ruled out.

Sildenafil:

- Caution should be exercised when prescribing sildenafil and CIPROGEN IV at the same time.

Zolpidem:

- Co -administration of CIPROGEN IV may increase blood levels of zolpidem; simultaneous use is not recommended (*see section 4.3*).

Phenytoin:

- Concomitant administration of CIPROGEN IV and phenytoin may result in increased or decreased serum phenytoin concentrations.

Methotrexate:

- If CIPROGEN IV and methotrexate are administered at the same time, the plasma levels of methotrexate may be increased. As this may lead to an increased risk of methotrexate-related toxic reactions, patients should be carefully monitored.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established (*see section 4.3*).

Breastfeeding

Safety in lactation has not been established (*see section 4.3)*.

4.7 Effects on ability to drive and use machines

The ability to drive a motor vehicle or operate machinery may be impaired by CIPROGEN IV.

This applies particularly in combination with alcohol.

4.8 Undesirable effects

Summary of the safety profile

Tabulated list of adverse reactions

Body System	Undesirable effect		
	Frequent	Less frequent	Frequency not known
Infections and Infestations:		Mycotic superinfections	
Blood and the lymphatic system disorders:		Eosinophilia, leucocytopenia, granulocytopenia, anaemia, thrombocytopenia, leucocytosis, thrombocytosis, haemolytic anaemia, altered	

		prothrombin values, neutropenia, pancytopenia (life-threatening), bone marrow depression (life-threatening).	
Immune system disorders:		Anaphylactic/anaphylactoid reactions occur (e.g. facial, vascular and laryngeal oedema, dyspnoea progressing to life-threatening shock), in some instances after the first administration. In these cases, CIPROGEN IV has to be discontinued and appropriate medical treatment instituted.	
Metabolism and nutrition disorders:		Hypoglycaemia, particularly in diabetic patients.	Hyperglycaemia, hypoglycaemic coma.
Psychiatric disorders:		Anxiety states, nightmares, confusion, hallucinations, psychotic reactions (even progressing to self-endangering behaviour), depression. In some instances, these reactions occurred after the first administration of ciprofloxacin. In these cases, CIPROGEN IV must be discontinued and the doctor informed immediately.	
Nervous system disorders:		Dizziness, headache, tiredness, nervousness, agitation, and trembling. Insomnia, peripheral paralgesia, sweating, unsteady gait, convulsions, increase in intracranial pressure. drowsiness, taste disturbances, paraesthesia, dysaesthesia,	

		hypoaesthesia, migraine, hyperaesthesia. In some instances, these reactions occurred after the first administration of ciprofloxacin. In these cases, CIPROGEN IV must be discontinued and the doctor informed immediately.	
Eye disorders:		Visual disturbances (e.g. diplopia, colour vision).	
Ear and labyrinth disorders:		Tinnitus, transient impairment of hearing – especially high frequencies.	
Cardiac disorders:	QTc interval prolongation	Tachycardia, flushing, migraine, syncope.	
Vascular disorders:		Vasodilation, hypotension, vasculitis, hot flush.	
Respiratory, thoracic and mediastinal disorders:		Dyspnoea (including asthma attacks), chest pain	
Gastrointestinal disorders:		Nausea, diarrhoea, vomiting, dyspepsia and abdominal pain, loss of appetite, indigestion, flatulence, pancreatitis. The development of severe and persistent diarrhoea may indicate pseudomembranous colitis, requiring immediate treatment. In such cases CIPROGEN IV must be discontinued and appropriate therapy initiated (e.g. vancomycin, orally 4 x 250 mg/day).	
Hepato-biliary disorders:		Elevated transaminase levels, bilirubinemia,	

		hepatic dysfunction, jaundice, (non-infectious) hepatitis, liver cell necrosis.	
Skin and subcutaneous tissue disorders:		Rashes, urticaria and photosensitivity (blisters, sensation of skin burning), erythema nodosum and erythema exsudativum multiforme (minor), Stevens-Johnson syndrome (SJS), Lyell's syndrome, punctate skin haemorrhages (petechiae), *haemorrhagic bullae* and papules with signs of vascular involvement (vasculitis),	DRESS (drug reaction with eosinophilia and systemic symptoms)
Musculoskeletal, connective tissue and bone disorders:		Joint pain, joint swelling, general feeling of weakness, and myalgia (which may be of special importance in patients with myasthenia gravis) and tendosynovitis. Achillotendinitis, partial or complete rupture of the achilles tendon occurred in predominantly elderly patients on treatment with systemic glucocorticoids (*see section 4.4*). At any sign of an achillotendinitis (or any tendonitis) (e.g. painful swelling) the administration of CIPROGEN IV should be discontinued and a doctor should be consulted.	
Renal and urinary disorders:		Crystalluria related to the use of CIPROGEN IV has been observed. Patients receiving CIPROGEN IV should be well hydrated and excessive alkalinity of	

		the urine should be avoided. Interstitial nephritis, transient renal impairment including transient renal failure, and haematuria, have been reported.	
General disorders and administrative site conditions:		Phlebitis or thrombophlebitis, local irritation and pain at the site of injection. 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 contraindicated unless the reactions recur or worsen. Malaise, fever, oedema, sweating, gait disturbances, general weakness.	
Investigations:		Increased alkaline phosphatase, abnormal prothrombin levels, increased lipase and amylase levels.	

Description of selected adverse reactions

Influence on laboratory parameters/ urinary sediment:

- 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), hypoglycaemia.

Other:

- Impaired taste and smell, hyperglycaemia.
- Hepatic necrosis, very seldom progressing to hepatic failure, has been reported.

Post-marketing experience:

- Cases of mitral valve and/or aortic valve regurgitation were reported in patients treated with oral fluoroquinolones. Due to insufficient post-marketing information in the reported cases, it is unknown whether fluoroquinolone use was the causative factor, or a contributory factor or played no role in the reported cases where mitral cases and/or aortic regurgitation was diagnosed.

Nervous system disorders:

- Peripheral neuropathy, polyneuropathy, anosmia (usually reversible when the medication is discontinued), stabbing pain.

Cardiac disorders:

- Ventricular arrhythmias, torsades de pointes.

Skin and subcutaneous tissue disorders:

- Acute generalised exanthematous pustulosis (AGEP).

Investigations:

- Increased INR (International Normalized Ratio) in patients treated with vitamin K antagonists.

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

- In overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8)*.
- In the event of acute, excessive oral overdosage, reversible renal toxicity has been reported.
- Apart from routine emergency measures, it is recommended to monitor renal function and to administer magnesium- or calcium-containing antacids which reduce the absorption of oral CIPROGEN IV.
- Only a small amount of ciprofloxacin (< 10 %) is removed from the body after haemodialysis or peritoneal dialysis.
- Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.1.1 Broad and medium spectrum antibiotics

J01MA02, Ciprofloxacin is a synthetic fluoroquinolone antibiotic.

It is bactericidal and acts by inhibiting the A subunit of DNA-gyrase which is essential in the reproduction of bacterial DNA.

5.2 Pharmacokinetic properties

After oral administration, ciprofloxacin plasma levels are dose-related and peak at 0,5 – 2 hours.

The absolute bioavailability is approximately 70 %. Protein binding is 40 %. Forty to fifty percent is excreted in urine as unchanged ciprofloxacin. Approximately 15 % of a single

dose is eliminated as metabolites. Elimination is primarily renal 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 is linear.

Micro-organisms resistant to ciprofloxacin:

Enterococcus faecium; Norcardia asteroides; Ureaplasma urealyticum; Peptostreptococcus species; *Peptococcus* species; Bacteroides; *Treponema pallidum*.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Chlorhydric acid 1N; glucose monohydrate; lactic acid.

6.2 Incompatibilities

CIPROGEN IV is compatible with various intravenous solutions, including sterile water for injections, 0,9 % sodium chloride solution, 5 % and 10 % dextrose solutions, 5 % dextrose with 0,225 % or 0,45 % sodium chloride solutions, Ringer's solution and Ringer's Lactate solution.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Before opening: Store at or below 25 ºC.

After opening immediate use is recommended.

Any remaining solution must be discarded.

Protect from light.

6.5 Nature and contents of container

100 ml and 200 ml transparent PVC bags.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

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

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris South Africa (Pty) Ltd.

4 Brewery Street,

Isando, Johannesburg,

1609

8 REGISTRATION NUMBER(S)

A40/20.1.1/0618

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

August 2021

10 DATE OF REVISION OF TEXT