Approved Professional information for Medicines for Human Use

FLOQIN IV 2 mg/mL (Solution for Infusion)

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

FLOQIN IV 2 mg/mL Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FLOQIN IV 2 mg/mL contains ciprofloxacin lactate equivalent to 2,0 mg ciprofloxacin per mL in 0,9 % sodium chloride solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion

Clear, colourless to slightly yellowish solution, free from foreign matters or particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FLOQIN IV 2mg/mL 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.

FLOQIN IV 2mg/mL 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 ofloxacin, 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.

FLOQIN IV 2 mg/m[ł]L 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 *Escherichia coli, Klebsiella pneumonia, Enterbacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilis influenzae and Haemophilus para-influenzae.*
- Severe and/or complicated urinary tract infections caused by *Escherichia coli, Klebsiella pneumonia, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Providencia retgeri, Morganella morganoo, Citrobacter diversus, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus epidermidis* and *Streptococcus faecalis.*
- Severe and/or complicated skin and soft tissue infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia staurtii Morganella morganii, Citrobacter freundii, Pseudomonas aeruginosa,* methicillin-sensitive *Staphylococcus aureus, Staphylococcus epidermidis* and *Streptococcus pyogenes*.
- Severe and/or complicated gastro-intestinal infections: Infective diarrhoea caused by E.*Coli, Campylobacter jejuni, Shigella flexneri* and *Shigella sonnei.*
- Severe and/or complicated bone infections**:** Osteomyelitis due to susceptible Gram-negative organisms.

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

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 FLOQIN IV 2 mg/mL. Therapy with FLOQIN IV 2 mg/mL 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 FLOQIN IV 2 mg/mL to contain and eradicate infection depends upon the severity and type of infection, immunological status, clinical response and bacteriological findings. This also includes the age, mass and renal function of the patient. The usual dose is 100 mg – 200 mg IV every 12 hours. For severe and/or complicated infections 400 mg may be administered every 12 hours (i.e. bd). Intravenous therapy should be discontinued as soon as oral Ciprofloxacin therapy can be substituted.

The normal duration of intravenous therapy is up to 7 days.

Cystic fibrosis:

In cystic fibrosis patients, the normal dose is 200 mg IV twice daily. The low body mass of these patients should, however, be taken into consideration when determining the dosage (5 - 10 mg/kg/day).

Method of administration

FLOQIN IV 2 mg/mL should be administered by intravenous infusion over a period of 60 minutes. Slow infusion into a large vein will minimize patient discomfort and reduce the risk of venous irritation. The infusion solution can be infused either directly or after mixing with the compatible infusion solutions.

The FLOQIN IV 2 mg/mL infusion solution is compatible with Ringer's solution, Lactated Ringer solution, Sodium chloride 9 mg/mL (0,9 %), Glucose 50 mg/mL (5 %) and 100 mg/mL (10 %), Fructose 50 mg/mL (5 %) and 100 mg/mL (10 %), Glucose 5 % with NaCl 0,225 % and Glucose 5 % with NaCl 0,45 % when FLOQIN IV 2 mg/mL infusion solutions are mixed with compatible infusion solutions, for microbiological reasons and light sensitivity these solutions should be administered shortly after admixture.

Impaired Renal or Liver Function:

In patients with reduced renal function the half-life of FLOQIN IV 2 mg/mL 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 ciprofloxacin serum levels provides the most reliable basis for dose adjustments.

Dose adjustment of ciprofloxacin for patients with kidney and/or liver insufficiency.

1. Kidney insufficiency:

1.1 CL_{cr} ≥ 31 mL/min/1,73m^2 ≤ 60 mL min/1,73m^2

Max 800 mg/day intravenously.

1.2 CL_{cr} ≤ 30 mL/min/1,73m^2

Max 400 mg/day intravenously

1.3 Impaired renal function and haemodialysis

As in 1.2 above; on dialysis days after dialysis

1 2. Impaired renal function and CAPD

Addition of ciprofloxacin infusion solution to the dialysate (intraperitoneal): 50 mg ciprofloxacin/litre dialysate administered 4 times a day.

2 3. Liver function disturbances: No dose adjustment

4. Liver and kidney insufficiency: As in 1.1 and 1.2 above

4.3 Contraindications

FLOQIN IV 2 mg/mL is contraindicated in children under 18 years and in growing adolescents, except where the benefits of treatment exceed the risks. Experimental evidence indicates that species variable reversible lesions of the cartilage of weight bearing joints has been seen in immature members of certain species.

FLOQIN IV 2 mg/mL is contraindicated under the following circumstances:

- In patients who have demonstrated hypersensitivity to ciprofloxacin, to other quinolones or to any of the excipients of FLOQIN IV 2 mg/mL (see section 2).
- With concomitant administration of tizanidine.
- 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.
- 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.
- Myasthenia gravis where alternative appropriate antibiotic choices are available to treat these patients.
- 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.
- Concomitant use of fluoroquinolones with ACE inhibitors/angiotensin receptor blockers in patients with moderate to severe renal impairment and in the elderly.
- FLOQIN IV 2 mg/mL is contraindicated in children less than 18 years.
- Patients with mitral valve and/or aortic valve regurgitation, unless no safer alternative antibiotic is available, has failed or is not well tolerated. A thorough cardiovascular examination, including an echocardiogram (ECG), should be performed before FLOQIN IV 2mg/mL is prescribed.

4.4 Special warnings and precautions for use

Severe infections and infections due to Gram positive or anaerobic bacteria.

FLOQIN IV 2mg/mL should not be used in staphylococcal infections and infections involving anaerobic bacteria.

Blood and lymphatic system

Side effects that may be potentially life-threatening are pancytopenia and bone marrow depression.

Methotrexate

Concurrent administration of methotrexate with FLOQIN IV 2 mg/m[ł]L may increase the concentration of methotrexate to toxic levels.

Central Nervous System (CNS)

FLOQIN IV 2 mg/mL 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 effects. Cases of status epilepticus have been reported (see Contraindications and Side Effects).

Psychiatric effects

Psychiatric reactions may occur even after first administration of FLOQIN IV 2 mg/mL. Depression or psychosis can progress to suicidal ideations/thoughts culminating in attempted suicide or completed suicide. In the occurrence of such cases, FLOQIN IV 2 mg/mL should be discontinued. Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination), have been reported in patients receiving ciprofloxacin, such as in FLOQIN IV 2 mg/mL. FLOQIN IV 2 mg/mL should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see section 4.3 Contraindications and 4.8 Side Effects).

Musculoskeletal system

Myasthenia gravis

The use of FLOQIN IV 2 mg/mL in patients with myasthenia gravis is contraindicated if appropriate antibiotic choices are available (see Contraindications). FLOQIN IV 2 mg/mL may exacerbate the symptoms of myasthenia gravis.

Tendinitis and tendon rupture

FLOQIN IV 2 mg/mL should not be used in patients with a history of tendon disorders, especially those related to previous exposure to

quinolone or fluoroquinolone use (see Contraindications).

Nevertheless, in some instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of FLOQIN IV 2 mg/mL.

Tendinitis and tendon rupture (especially of the Achilles tendon), sometimes bilateral, may occur with ciprofloxacin (such as in FLOQIN IV 2 mg/mL), even within the first 48 hours of treatment. Inflammation and ruptures of tendon may occur even up to several months after discontinuation of therapy. The risk of tendinopathy may be increased in elderly patients or in patients being concomitantly treated with corticosteroids. At any sign of tendinitis (e.g. painful swelling, inflammation), treatment with FLOQIN IV 2 mg/mL should be discontinued. Care should be taken to keep the affected limb at rest.

Photosensitivity

FLOQIN IV 2 mg/mL has been shown to cause photosensitivity reactions.

Patients taking FLOQIN IV 2 mg/mL should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment.

Cardiac disorders

Aortic aneurysm and dissection

There is some evidence of an increased risk of aortic aneurysm and 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 dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a medical practitioner in an emergency department.

QT interval prolongation

- FLOQIN IV 2 mg/mL has been associated with QT prolongation (see section 4.3 Contraindications and 4.8 Side effects).
- Concomitant use of FLOQIN IV 2 mg/mL 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 and III antidysrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.5 Interactions) or congenital long QT syndrome, risk of Torsades de Pointes, uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia) and cardiac disease such as heart failure, myocardial infarction or bradycardia.
- Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including FLOQIN IV 2 mg/mL, in these populations.
- A pre-treatment ECG and frequent follow up ECG monitoring is mandatory with concomitant use to determine whether concomitant use is contraindicated.
- There is some evidence of an increased risk of aortic aneurysm and/or dissection after intake of fluoroquinolones, particularly in the elderly population. Fluoroquinolones, such as FLOQIN IV 2mg/mL should only be used in patients at risk if no other treatment options are available (see section 4.3 Contraindications). Patients at risk are patients with a positive family history of aneurysmal disease, pre-existing aortic disease and/or dissection or other risk factors or conditions predisposing to aortic aneurysm and dissection e.g. Marfan syndrome, Vascular Ehlers Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension and known atherosclerosis. In case of sudden abdominal, chest or back pain, patients should be advised to immediately go to their medical practitioner or a hospital emergency department.

Concomitant use with ACE inhibitors/angiotensin receptor blockers (ARBs)

Concomitant use of fluoroquinolones, such as FLOQIN 2mg/mL**,** with ACE inhibitors/angiotensin receptor blockers (ARBs) may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3 Contraindications). Renal function should be assessed before initiation of treatment, and monitored during treatment with fluoroquinolones and ACE inhibitors/angiotensin receptor blockers.

Children and adolescents

FLOQIN 2 mg/mL is contraindicated in children less than 18 years (see section 4.3 Contraindications).

Hypoglycaemia

Ciprofloxacin, as contained in FLOQIN IV 2 mg/mL, hypoglycemia has been reported most often in diabetic patients, predominantly in the elderly population. In all diabetic patients, especially those receiving concomitant treatment with an oral hypoglycaemic medicine or with insulin, careful monitoring of blood glucose is recommended.

Gastrointestinal system

The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment. In such cases, FLOQIN IV 2 mg/m[ɬ]L should immediately be discontinued, and an appropriate therapy initiated.

Anti-peristaltic medicines are contraindicated in this situation.

Renal and urinary system

Crystalluria related to the use of FLOQIN IV 2 mg/m[ɬ]L has been reported. Patients receiving FLOQIN IV 2 mg/m[ɬ]L should be well hydrated and excessive alkalinity of the urine should be avoided.

Impaired renal function

Since ciprofloxacin is largely excreted unchanged via the renal pathway, dose adjustment is needed in patients with impaired renal function, (see 4.2 Posology and method of administration), to

avoid an increase in adverse drug reactions due to accumulation of ciprofloxacin.

Hepatobiliary system

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with FLOQIN IV 2 mg/mL. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.

Glucose-6-phosphate dehydrogenase deficiency

Haemolytic reactions have been reported with FLOQIN IV 2 mg/mL in patients with glucose-6-phosphate dehydrogenase deficiency. FLOQIN IV 2 mg/mL should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

Injection site reaction

Local intravenous site reactions have been reported with the intravenous administration of FLOQIN IV 2 mg/mL. These reactions are more frequent if the infusion time is 30 minutes or less. 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.

Severe infections and mixed infections with Gram-positive and anaerobic pathogens

FLOQIN IV 2 mg/mL monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections, FLOQIN IV 2 mg/mL must be co-administered with other appropriate antibacterial medicines.

Streptococcal infections (including *Streptococcus pneumoniae*)

Ciprofloxacin, such as FLOQIN IV 2 mg/mL is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Hypersensitivity

Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose of FLOQIN IV 2 mg/mL and may be life threatening. If such a reaction occurs, FLOQIN IV 2 mg/mL should be discontinued and adequate medical treatment should be administered.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be

consulted immediately.

Resistance

During or following a course of treatment with ciprofloxacin, such as in FLOQIN IV 2 mg/mL, bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.

Cytochrome P450

Ciprofloxacin, such as in FLOQIN IV 2 mg/mL, inhibits CYP1A2 and thus may cause increased serum concentrations of concomitantly administered medicines metabolised by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine, duloxetine, agomelatine). Therefore, patients taking these medicines concomitantly with FLOQIN IV 2 mg/mL should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5). Co-administration of ciprofloxacin and tizanidine is contraindicated (see section 4.3 Contraindications).

Interaction with tests

The *in vitro* activity of FLOQIN IV 2 mg/mL against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking FLOQIN IV 2 mg/mL.

Influence on laboratory parameters/urinary sediment

Hypoglycaemia is one of the manifestations that may occur with taking FLOQIN IV 2mg/mL.

Excipients

FLOQIN IV 2 mg/mL contains sodium (900 mg/100 mL and 1800 mg/200 mL). The sodium content should be taken into account in patients on a controlled sodium diet, patients with congestive heart failure, renal failure, nephrotic syndrome, etc.

4.5 Interaction with other medicines and other forms of interaction

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

Effects of other medicines on FLOQIN IV 2 mg/mL

Medicines known to prolong QT interval

FLOQIN IV 2 mg/mL, like other fluoroquinolones, should be used with caution in patients receiving medicines known to prolong QT interval (e.g. Class IA and III anti-dysrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4 Special warnings and precautions for use).

Probenecid

Probenecid interferes with renal secretion of FLOQIN IV 2 mg/mL.

Co-administration of probenecid and ciprofloxacin increases FLOQIN IV 2 mg/mL serum concentrations.

Effects of FLOQIN IV 2 mg/mL on other medicines:

Tizanidine

Tizanidine must not be administered together with FLOQIN IV 2 mg/mL (see section 4.3 Contraindications). An increase in serum tizanidine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) has been observed when tizanidine is given concomitantly with ciprofloxacin, such as in FLOQIN IV 2 mg/mL. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of FLOQIN IV 2 mg/mL, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see WARNINGS and SPECIAL PRECAUTIONS).

Theophylline

Concurrent administration of FLOQIN IV 2 mg/mL and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may be life threatening or fatal.

During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary.

Other xanthine derivatives

On concurrent administration of FLOQIN IV 2 mg/mL and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

Phenytoin

Simultaneous administration of FLOQIN IV 2 mg/mL and phenytoin may result in increased or reduced serum levels of phenytoin and monitoring of phenytoin levels is recommended.

Ciclosporin

A transient rise in the concentration of serum creatinine was observed when FLOQIN IV 2 mg/mL and ciclosporin containing medicines were administered simultaneously. Therefore, it is frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.

Vitamin K antagonists

Simultaneous administration of FLOQIN IV 2 mg/mL with a vitamin K antagonist may augment its anti-coagulant effects. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of FLOQIN IV 2 mg/mL to the increase in INR (international normalised ratio) is difficult to assess. The INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with a vitamin K antagonist (e.g., warfarin or fluindione).

Duloxetine

Concomitant use of duloxetine with strong inhibitors of the CYP450 1A2 isozyme such as fluvoxamine, may result in an increase of AUC and C_{max} of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin such as FLOQIN IV 2 mg/mL, similar effects can be expected upon concomitant administration.

Ropinirole

Concomitant use of ropinirole with ciprofloxacin, such as FLOQIN IV 2 mg/mL, a moderate inhibitor of the CYP450 1A2 isozyme, has been shown to increase C_{max} and AUC of ropinirole by 60 % and 84 %, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with FLOQIN IV 2 mg/mL.

Lidocaine

Concomitant use of lidocaine containing medicines with ciprofloxacin, such as in FLOQIN IV 2 mg/mL, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22 %. Although lidocaine treatment was well tolerated, a possible interaction with ciprofloxacin, associated with side effects, may occur upon concomitant administration of lidocaine and FLOQIN IV 2 mg/mL.

Clozapine

Concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, showed an increase in serum concentrations of clozapine and N-desmethylclozapine by 29 % and 31 %, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin, such as in FLOQIN IV 2 mg/mL, are advised.

Sildenafil

An approximately two-fold increase in C_{max} and AUC of sildenafil was observed after an oral dose of 50 mg sildenafil was given concomitantly with 500 mg ciprofloxacin. Therefore, caution should be used prescribing ciprofloxacin, such as FLOQIN IV 2 mg/mL concomitantly with sildenafil.

Agomelatine

Fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedly inhibits the metabolism of agomelatine resulting in a 60-fold increase of agomelatine exposure. Although no clinical data are available for a possible interaction with ciprofloxacin, such as in FLOQIN IV 2 mg/mL (a moderate inhibitor of CYP450 1A2) similar effects can be expected upon concomitant administration (see section 4.3 Special warnings and precautions for use).

Zolpidem

Co-administration of ciprofloxacin, such as in FLOQIN IV 2 mg/mL**,** may increase blood levels of zolpidem, and concurrent use is not recommended.

General

Concomitant administration of FLOQIN IV 2 mg/mL and omeprazole results in a 20 % reduction of the C_{max} and AUC of FLOQIN IV 2 mg/mL.

Concomitant administration of the nonsteroidal anti-inflammatory drug fenbufen with quinolones has been reported to increase the risk of central nervous system stimulation and convulsive seizures.

Concomitant administration of FLOQIN IV 2 mg/mL and glibenclamide can intensify the action of glibenclamide (hypoglycaemia).

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety during pregnancy has not been established. Available data on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones (such as ciprofloxacin, as contained in FLOQIN IV 2 mg/mL, effects on immature cartilage have been observed, thus, it cannot be excluded that FLOQIN IV 2 mg/mL could cause damage to articular cartilage in the human immature organism / foetus.

Lactation

FLOQIN IV 2 mg/mL is excreted in breast milk. Due to the potential risk of articular damage, FLOQIN IV 2 mg/mL should not be used during breastfeeding.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, FLOQIN IV 2 mg/mL may affect reaction time. Therefore, the ability to drive or to operate machinery may be impaired.

4.8 Undesirable effects

The table below shows all adverse drug reactions (ADRs) observed with the use of FLOQIN IV 2mg/mL

System Organ Class	Frequent	Less frequent	Frequency not known
Infections and Infestations		Mycotic super-infections	
Blood and Lymphatic System Disorders		Eosinophilia, leukopenia, anaemia, neutropenia, leukocytosis, thrombocytopenia, thrombocytaemia, haemolytic anaemia, agranulocytosis, pancytopenia (life-threatening), bone marrow depression (life-threatening)	
Immune System Disorders		Allergic reaction, allergic oedema / angiooedema, anaphylactic reaction, anaphylactic shock (life-threatening), serum sickness-like reaction	

Endocrine disorders			Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Metabolism and Nutrition Disorders		Decreased appetite hyperglycaemia, hypoglycaemia	Hypoglycaemic coma
Psychiatric Disorders*		Psychomotor hyperactivity / agitation, confusion and disorientation, anxiety reaction, abnormal dreams, depression (potentially culminating in suicidal ideations / thoughts or suicide attempts and completed suicide), hallucinations, psychotic reactions (potentially culminating in suicidal ideations / thoughts or suicide attempts and completed suicide, mania, hypomania	Mania, incl. hypomania

Nervous System Disorders*		Headache, dizziness, sleep disorders, taste disorders, Par- and Dysaesthesia, hypoaesthesia, tremor, seizures (including status epilepticus), vertigo, migraine disturbed coordination, gait disturbance, olfactory nerve disorders, intracranial hypertension and pseudotumor cerebri, peripheral neuropathy and polyneuropathy.	Peripheral neuropathy and polyneuropathy
Eye Disorders*		Visual disturbances, (e.g. diplopia), visual colour distortions	
Ear and Labyrinth Disorders*		Tinnitus, hearing loss / hearing impaired	

Cardiac Disorders		Tachycardia	Ventricular arrhythmia, torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged
Vascular Disorders		Vasodilatation, hypotension, syncope, vasculitis	
Respiratory, Thoracic and Mediastinal Disorders		Dyspnoea (including asthmatic condition)	
Gastrointestinal Disorders	Nausea, diarrhoea,vomiting,	Gastrointestinal and abdominal pains, dyspepsia, flatulence, antibiotic associated colitis (in some cased with possible fatal outcome), pancreatitis	
Hepatobiliary Disorders	Transient increase in transaminases	Increased bilirubin, hepatic impairment, cholestatic icterus, hepatitis,	

		liver necrosis (in some cases progressing to life-threatening hepatic failure)	
Skin and Subcutaneous Tissue Disorders	Rash	Pruritus, urticaria, photosensitivity reactions, petechiae, erythema multiform, erythema nodosum, Steven-Johnson syndrome (potentially life-threatening), toxic epidermal necrolysis (potentially life-threatening)	Acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and Connective Tissue Disorders*		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain), arthralgia, myalgia, arthritis, increased muscle tone and cramping, muscular weakness, tendinitis, tendon rupture (predominantly	

		Archilles tendon), exacerbation of symptoms of myasthenia gravis	
Renal and Urinary Disorders		Renal impairment, renal failure, haematuria, crystalluria, tubulointestinal nephritis	
General Disorders and Administration Site Conditions*	Injection and infusion site reactions	Asthenia, fever, oedema, sweating (hyperhydrosis)	
Investigations		Increase in blood alkaline phosphatase, increased amylase	Increased International normalised ratio (INR) (in patients treated with Vitamin K antagonists)

*Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see section 4.4, Special warnings and precautions for use).

Paediatric population

The incidence of arthropathy (arthralgia, arthritis), mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.3 Warnings and special precautions for use).

4.9 Overdose

Symptoms of over-dose include dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

In the event of acute, excessive oral overdosage, reversible renal toxicity has been reported. Therefore, 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 FLOQIN IV 2 mg/m[l]L. Only a small amount of FLOQIN IV 2 mg/mL (< 10 %) is removed from the body after haemodialysis or peritoneal dialysis. Treatment should be symptomatic and supportive. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01 MA02

Mechanism of action

Ciprofloxacin is a fluoroquinolone antibacterial medicine. The bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

The Following Are Inherently Resistant Organisms

Aerobic Gram-positive micro-organisms

Actinomyces

Enteroccus faecium

Listeria monocytogenes

Aerobic Gram-negative micro-organisms

Stenotrophomonas maltophilia

Anaerobic micro-organisms

Treponema pallidum

Other micro-organisms

Mycoplasma genitalium

Ureaplasma urealitycum.

5.2 Pharmacokinetic properties

Absorption

Following an intravenous infusion of ciprofloxacin the mean maximum serum concentrations were achieved at the end of infusion. Pharmacokinetics of ciprofloxacin were linear over the dose range up to 400 mg administered intravenously.

Distribution

Distribution of ciprofloxacin is wide and the volume of distribution high, indicating extensive tissue penetration. Ciprofloxacin is present in lung, skin, fat, muscle, cartilage and bone. It is also present in active form in the saliva, nasal and bronchial secretions, sputum, skin blister fluid, lymph, peritoneal fluid, bile secretions, prostatic secretions, cerebrospinal fluid and the aqueous humor.

Elimination

Protein binding is low. 40 % to 50 % is excreted in urine as unchanged ciprofloxacin. 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.

Paediatric population

The pharmacokinetic data in paediatric patients are limited.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactic acid,

Sodium chloride,

Water for injection.

6.2 Incompatibilities

Unless compatibility with other infusion solutions/ medicines has been confirmed, the infusion solution must always be administered separately. The visual signs of incompatibility are e.g. precipitation, clouding and discolouration.

Incompatibility appears with all infusion solutions/ medicines that are physically or chemically unstable at the pH of the solution (e.g. penicillins, heparin solutions), especially adjusted to an alkaline pH (pH of the ciprofloxacin infusion solutions: 3,9 - 4,5).

Any remaining solution should be discarded.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

The glass bottle must be stored in the outer carton until required for use.

FLOQIN IV 2 mg/mL: After the infusion of the required dose any remaining solution should be discarded. FLOQIN IV 2 mg/mL light-sensitive and should always be stored in the cardboard outer carton. No special precautions are, however, required during the 60-minute infusion period.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

FLOQIN IV 200 mg/100 mL:

Uncoloured glass bottles type I, stoppered with bromobutyl rubber closures sealed with aluminium caps. One glass bottle is packaged in an outer carton.

FLOQIN IV 400 mg/200 mL:

Uncoloured glass bottles type I, stoppered with bromobutyl rubber closures sealed with aluminium caps. One glass bottle is packaged in an outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBER(S)

50/20.1.1/1035

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

20 March 2018

10. DATE OF REVISION OF THE TEXT

27 January 2023