1.3.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS: **S4**

PROPRIETARY NAME AND DOSAGE FORM:

ADCO CIPROFLOXACIN 2 mg/ml

Infusion (Parenteral)

COMPOSITION:

ADCO CIPROFLOXACIN 2 mg/ml contains 2 mg ciprofloxacin per ml in 0,9 % sodium chloride solution.

List of inactive ingredients: Lactic acid, Water for injections.

Sugar free

CATEGORY AND CLASS:

A 20.1.1 Broad and medium spectrum antibiotics

PHARMACOLOGICAL ACTION:

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.

Pharmacokinetics:

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 to 5 hours. The elimination kinetics are linear.

Micro-organisms resistant to ciprofloxacin:

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

INDICATIONS:

ADCO CIPROFLOXACIN 2 mg/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.

ADCO CIPROFLOXACIN 2 mg/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 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.

ADCO CIPROFLOXACIN 2 mg/ml is indicated for the treatment of the following infections, when caused by susceptible organisms, 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 gastro-intestinal 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 **ADCO CIPROFLOXACIN 2 mg/ml**. Therapy with **ADCO CIPROFLOXACIN 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.

CONTRAINDICATIONS:

- **ADCO CIPROFLOXACIN 2 mg/ml** is contraindicated in patients with a history of hypersensitivity to ciprofloxacin, any other quinolones, or any of the inactive ingredients.
- 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.
- 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.
- 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.
- Concomitant use of fluoroquinolones with ACE inhibitors/angiotensin receptor blockers in patients with moderate to severe renal impairment and in the elderly.

ADCO CIPROFLOXACIN 2 mg/ml is contraindicated in children under the age of 18 years. Experimental evidence indicates lesions of the cartilage of weight-bearing joints in immature members of certain animal species.

WARNINGS AND SPECIAL PRECAUTIONS:

Crystalluria related to the use of **ADCO CIPROFLOXACIN 2 mg/ml** has been observed. Patients receiving **ADCO CIPROFLOXACIN 2 mg/ml** should be well hydrated and excessive alkalinity of the urine should be avoided.

In the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside must be administered concomitantly (see "**DOSAGE AND DIRECTIONS FOR USE**").

The development of severe and persistent diarrhoea may indicate pseudomembranous colitis, requiring immediate treatment. In such cases **ADCO CIPROFLOXACIN 2 mg/ml** must be discontinued and appropriate therapy initiated (e.g. vancomycin, orally 4 x 250 mg/day.)

Anaphylactic reactions can occur in some instances after the first administration. In these cases, **ADCO CIPROFLOXACIN 2 mg/ml** has to be discontinued and appropriate medical treatment instituted.

Long-term or repeated administration of **ADCO CIPROFLOXACIN 2 mg/ml** can lead to super infections with resistant bacteria or fungi.

Exposure to strong sunlight or sunlamp should be avoided.

Care is necessary in patient with impaired hepatic or renal function, G6PD deficiency and myasthenia gravis (see C**ONTRAINDICATIONS** and **SIDE EFFECTS**).

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

ADCO CIPROFLOXACIN 2 mg/ml should not be used in staphylococcal infections and infections involving anaerobic bacteria.

Musculoskeletal System:

- The use of **ADCO CIPROFLOXACIN 2 mg/ml** in patients with myasthenia gravis is contraindicated if alternative appropriate antibiotic choices are available (see **CONTRAINDICATIONS**). **ADCO CIPROFLOXACIN 2 mg/ml** may exacerbate the symptoms of myasthenia gravis.
- Cases of achillotendinitis have been observed. Partial or complete rupture of the Achilles tendon occurred in predominantly elderly patients on treatment with systemic glucocorticoids. At any sign of an achillotendinitis (or any tendonitis) (e.g. painful swelling) the administration of **ADCO CIPROFLOXACIN 2 mg/ml** should be discontinued and a medical practitioner should be consulted. (see **CONTRAINDICATIONS**)
- **ADCO CIPROFLOXACIN 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**)

Psychotic reaction:

- Psychotic reaction (even progressing to self–endangering behaviour), may occur. In some instances, these reactions occurred after the first administration of ciprofloxacin. In these cases, **ADCO CIPROFLOXACIN 2 mg/ml** must be discontinued and the medical practitioner informed immediately. (see **CONTRAINDICATIONS** and **SIDE EFFECTS**)

Cardiac disorders:

- 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 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, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, knows atherosclerosis)

- In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a medical practitioner in an emergency department of a hospital.
- **ADCO CIPROFLOXACIN 2 mg/ml** has been associated with QT prolongation. (See "**CONTRAINDICATIONS**" and "**SIDE EFFECTS**"). Concomitant use of **ADCO CIPROFLOXACIN 2 mg/ml** with medicines resulting in 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 Ill antidysrhythmics, tricyclic antidepressants, macrolides, anti-psychotics) (see **INTERACTIONS)** 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.
- 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, **ADCO CIPROFLOXACIN 2 mg/ml** should only be used in patients at risk if no other treatment options are available (see CONTRAINDICATIONS)
- Patients at risk are patients with a positive family history of aneurysmal disease, pre-existing aortic disease and/or dissection or other 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 consult a medical practitioner in an emergency department of a hospital.
- There is some evidence, although inconclusive, of a possible association between 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 **CONTRAINDICATIONS**)

- Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients. (see **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:

- **ADCO CIPROFLOXACIN 2 mg/ml** is contraindicated in children less than 18 years. In children arthropathy is reported to occur commonly (see additional information on special populations)

Nervous system:

- **ADCO CIPROFLOXACIN 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**).

Influence on laboratory parameters/urinary sediment:

Hypoglycaemia may occur.

Ability to drive or operate machinery:

The ability to drive motor vehicle or operate machinery may be impaired by ADCO CIPROFLOXACIN 2 mg/ml, especially when alcohol is also taken.

INTERACTIONS:

Concurrent administration of **ADCO CIPROFLOXACIN 2 mg/ml** 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.

Concomitant administration of nonsteroidal anti-inflammatory medicines NSAIDs with **ADCO CIPROFLOXACIN 2 mg/ml** may increase the risk of central nervous system stimulation and seizures.

Monitoring of serum creatinine concentrations is advised in patients on concomitant ciclosporin therapy, as transient increases in serum creatinine concentrations have been observed. The simultaneous administration of **ADCO CIPROFLOXACIN 2 mg/ml** and warfarin may lead to warfarin toxicity; therefore, the INR should be closely monitored.

Concurrent administration of **ADCO CIPROFLOXACIN 2 mg/ml** and glibenclamide can potentiate the action of glibenclamide, leading to hypoglycaemia.

Probenecid interferes with renal excretion of **ADCO CIPROFLOXACIN 2 mg/ml**. Co-administration of probenecid and **ADCO CIPROFLOXACIN 2 mg/ml** increases the **ADCO CIPROFLOXACIN 2 mg/ml** serum concentrations.

Concurrent administration of methotrexate may increase the concentration of methotrexate to toxic levels.

Serum levels of phenytoin may be increased or decreased.

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

HUMAN REPRODUCTION

Safety in pregnancy and lactation has not been established (see “CONTRAINDICATIONS”).

DOSAGE AND DIRECTIONS FOR USE:

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

ADCO CIPROFLOXACIN 2 mg/ml IV

Dosage and duration of treatment:

The dosage of **ADCO CIPROFLOXACIN 2 mg/ml** 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.

Adults: The usual dose is 100 mg to 200 mg IV 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 ciprofloxacin 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 IV every 12 hours. The low body mass of these patients should however, be taken into consideration when determining dosage (5 to 10 mg/ kg/day).

Directions of intravenous administration:

ADCO CIPROFLOXACIN 2 mg/ml 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 directly.

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 impaired 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. **Renal impairment:**

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 Max 400 mg/day intravenously.

1.3. Impaired renal function and haemodialysis As in 1.2 above; after dialysis; on dialysis days

2. Renal impairment and CAPD (chronic ambulatory peritoneal dialysis):

2.1. Addition of **ADCO CIPROFLOXACIN 2 mg/ml** 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.

SIDE-EFFECTS

Side effects have been ranked according to frequency within each organ class. The following side effects have been reported and may occur with **ADCO CIPROFLOXACIN 2 mg/ml**:

Gastro-intestinal disorders:

Frequent: Nausea, diarrhoea, vomiting,

Less frequent: Dyspepsia, abdominal pain, dry mouth, anorexia, increased appetite, flatulence and pseudomembranous colitis.

Eye disorders:

Less frequent: Visual disturbances (e.g. diplopia, colour vision).

Ear and labyrinth disorders:

Less frequent: Tinnitus, transient impairment of hearing–especially at high frequencies.

Blood and lymphatic system disorders:

The following side effects have been reported and frequencies are unknown:

Eosinophilia, anaemia, leucocytopenia, granulocytopenia, thrombocytopenia, leucocytosis, thrombocytosis.

Haemolyticanaemia, altered prothrombin values, bone marrow depression, panaytopenia.

Skin and subcutaneous tissue disorders:

Less frequent: Rashes, urticaria and photosensitivity, blisters, sensation of skin burning, erythema nodosum and erythema exsudativum multiforme (minor), Stevens-Johnson syndrome, Lyell's syndrome, punctate skin haemorrhages (petechiae), haemorrhagic bullae and papules with signs of vascular involvement (vasculitis).

Nervous system disorders:

Less frequent: Dizziness, headache anxiety state.

Tiredness, nervousness, trembling ataxia somnolence, hyperesthesia, hypertonia, hypoesthesia, insomnia, peripheral paralgesia, sweating, unsteady gait, convulsions, increase in intracranial pressure, nightmares.

Psychiatric disorders:

Less frequent: Hallucinations, agitation, confusion, psychotic reactions (even progressing to self-endangering behaviour), depression.

In some instances, these reactions occurred after the first administration of ciprofloxacin. In these cases, **ADCO CIPROFLOXACIN 2 mg/ml** must be discontinued and the medical practitioner informed immediately.

Musculoskeletal connective tissue and bone disorders:

Less frequent: Joint pain, joint swelling, general feeling of weakness, arthralgia and myalgia (which may be of special importance in patients with myasthenia gravis) and tendosynovitis have been observed

Cardiovascular disorders:

Less frequent: Tachycardia, flushing, migraine, syncope hypotension.

Renal and urinary disorders:

Less frequent: Interstitial nephritis, transient renal impairment including transient renal failure, and haematuria, has been reported.

Crystalluria related to the use of ciprofloxacin has been observed.

Immune system disorders:

The following side effects have been reported and frequencies are unknown:

Anaphylactic/anaphylactoid reactions can occur (e.g. facial, vascular and laryngeal oedema, dyspnoea progressing to life-threatening shock).

General disorders and administration site conditions:

Less frequent: 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.

Investigations:

Less frequent: 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).

Infections and Infestations:

Less frequent: Moniliasis.

Endocrine disorders:

Less frequent: Impaired taste and smell, hyperglycaemia.

Hepato-biliary disorders:

Less frequent: Hepatic necrosis, very seldom progressing to hepatic failure, cholestatic jaundice.

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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Only a small amount of ciprofloxacin (< 10 %) is removed from the body after haemodialysis or peritoneal dialysis.

Treatment is symptomatic and supportive.

IDENTIFICATION:

A clear, pale yellow solution free from visible particles.

PRESENTATION:

50 ml clear and colourless PVC infusion bag containing 50 ml solution.

100 ml clear and colourless PVC infusion bag containing 50 ml or 100 ml solution.

250 ml clear and colourless PVC infusion bag containing 200 ml solution.

The bags are over-pouched with an aluminium-polyester over-wrapping.

STORAGE INSTRUCTIONS:

Store at below 25 °C. Protect from light.

KEEP OUT OF REACH OF CHILDREN

Do not administer the solution if visible particles are present, or if the solution is cloudy. The solution must be infused immediately after opening and any portion remaining after infusion must be discarded. **ADCO CIPROFLOXACIN 2 mg/ml** may not be refrigerated or frozen.

REGISTRATION NUMBER:

A39/20.1.1/0646

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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