דצמבר 2021

רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,

חברת פרופארם בע"מ מודיעה על העדכונים הבאים בעלון לרופא של התכשיר:

CIPROFLOXACIN I.V ALTAN 2 MG/ML
ציפרופלוקסצין I.V אלטן 2 מ"ג/מ"ל

חומר פעיל: CIPROFLOXACIN 2 MG/ML
צורת מינון: SOLUTION FOR INFUSION
צורת מתן: I.V.

עדכונים בעלון לרופא

<u>התויה כפי שאושרה בתעודת הרישום:</u>

Adults:
Broad spectrum antibiotic for infections caused by ciprofloxacin sensitive pathogens.

Children and adolescents:
•Broncho-pulmonary infections in cystic fibrosis caused by Pseudomonas aeruginosa
•Complicated urinary tract infections and pyelonephritis
•Inhalation anthrax (post-exposure prophylaxis and curative treatment)
Ciprofloxacin may also be used to treat severe infections in children and adolescents when there is no other alternative.
Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

<u>ברצונינו להודיע שהעלון לרופא עודכן, בפירוט שלהלן כלולים העדכונים העיקריים בלבד(תוספות /שינויים מסומנים באדום והחמרות/מידע חדש על רקע צהוב):</u>

4.2 Posology and method of administration

[…]

<u>Adults</u>

Indications		**Daily dose in mg**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
~~Acute pyelonephritis~~Urinary tract infections (see section 4.4)	Acute and complicated pyelonephritis	400 mg twice daily to 400 mg three times a day	7 to 21 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
~~Complicated urinary tracked infections~~		~~400 mg twice daily to 400 mg three times a day~~	~~7 to 14 days~~
~~Bacterial prostatitis~~	Bacterial prostatitis	400 mg twice daily to 400 mg three times a day	2 to 4 weeks (acute)
Genital tract infections	Epididymo-orchitis and pelvic inflammatory diseases including cases due to susceptible *Neiserria gonorrhoeae*	400 mg twice daily to 400 mg three times a day	at least 14 days

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Infections of the skin and soft tissue caused by Gram-negative bacteria	400 mg twice daily to 400 mg three times a day	7 to 14 days

[…]

4.4 Special warnings and precautions for use

The use of ciprofloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with ciprofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see section 4.3).

[…]

Genital tract infections

Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone- resistant *Neisseria gonorrhoeae* isolates. For *epididymo-orchitis and pelvic inflammatory diseases, empirical ciprofloxacin* Ciprofloxacin should only be consideredadministered in combination with another appropriate antibacterial agent (e.g. a cephalosporin) unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Urinary tract infections

Resistance to fluoroquinolones of Escherichia coli - the most common pathogen involved in urinary tract infections - varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in Escherichia coli to fluoroquinolones.

Complicated urinary tract infections and pyelonephritis

Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.
Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections

Other severe infections in accordance with official guidance, or after careful benefit- risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use. The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.

Hypersensitivity

Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.
Prolonged, disabling and potentially irreversible serious adverse drug reactions Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors.
Ciprofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

Tendinitis and tendon rupture

~~*Musculoskeletal system:*~~

[…]

Tendinitis and tendon rupture (especially ~~Achilles tendon~~but not limited to Achilles tendon), sometimes bilateral, may ~~occur with ciprofloxacin~~as early ~~as soon~~as ~~the first~~within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment (see section 4.8). The risk of tendinitis and tendon rupture is ~~tendinopathy~~

~~may be~~increased in ~~elderly~~ older patients, ~~or in~~ patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.
~~concomitantly treated with corticosteroids (see section 4.8).~~
At ~~any~~ the first sign of tendinitis (e.g. painful swelling, inflammation), the treatment with ciprofloxacin ~~treatment~~should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

Patients with myasthenia gravis
~~. Care should be taken to keep the affected limb at rest.~~
Ciprofloxacin should be used with caution in patients with myasthenia gravis, because symptoms can be exacerbated (see section 4.8).

Aortic aneurysm and dissection, and heart valve regurgitation/incompetence
Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake of fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.8).
Therefore, fluoroquinolones should only be used after a careful benefit/risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease or congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection or heart valve disease, or in presence of other risk factors or conditions predisposing
- for both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis) or additionally
- for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjogren's syndrome) or additionally
- for heart valve regurgitation/incompetence (e.g. infective endocarditis).

The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.
In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.
Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

Vision disorders
If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

[…]

Seizures
Ciprofloxacin like other ~~Central nervous system:~~
Quinolones are known to trigger seizures or lower the seizure threshold. Cases of status epilepticus have been reported. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8).

Peripheral neuropathy
Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypoaesthesia, dysaesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with ciprofloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition (see section 4.8).

Psychiatric reactions

Psychiatric reactions may occur even after ~~the~~first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to ~~endangering~~suicidal ideations/thoughts culminating in attempted suicide or completed suicide. If depression, psychotic reactions, suicide-related thoughts or ~~self-endangering~~ behaviour~~In these cases~~occur, ciprofloxacin 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.~~

~~Ciprofloxacin 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 4.8~~

[…]

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported (see section 4.8), usually in elderly diabetic patients, receiving concomitant treatment with an oral hypoglycaemic agent (e.g. glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Impaired renal function

Since ciprofloxacin is largely excreted unchanged via renal pathway dose adjustment is needed in patients with impaired renal function as described in section 4.2 to avoid an increase in adverse drug reactions due to accumulation of ciprofloxacin.

[…]

Cytochrome P450

Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine~~Co-administration of ciprofloxacin and tizanidine is contra- indicated,~~ duloxetine, agomelatine. Therefore, patients taking these substances concomitantly with ciprofloxacin 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.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other ~~medicinal~~products on ciprofloxacin:

Drugs known to prolong QT interval

Ciprofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4).

[…]

Cyclosporin

A transient rise in the concentration of serum creatinine was observed when ciprofloxacin and cyclosporin containing medicinal products were administered simultaneously. Therefore, it is frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.

[…]

Duloxetine

In clinical studies, it was demonstrated that concomitant use of duloxetine with strong inhibitors of the CYP450 1A2 isozyme such as fluvoxamine, may result in an increase of AUCand Cmax of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration (see section 4.4).

[…]

Lidocaine
It was demonstrated in healthy subjects that concomitant use of lidocaine containing medicinal products with ciprofloxacin, 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.

[…]

Sildenafil
Cmax and AUC of sildenafil were increased approximately twofold in healthy subjects after anoral dose of 50 mg given concomitantly with 500 mg ciprofloxacin. Therefore, caution should be used prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.

Agomelatine
In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP4501A2 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, a moderate inhibitor of CYP450 1A2, similar effects can be expected upon concomitant administration (see section 4.4).

Zolpidem
Co-administration of ciprofloxacin may increase blood levels of zolpidem, concurrent use isnot recommended.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, ~~some of the adverse drug reactions associated with~~ ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired~~in rare cases~~.

4.8 Undesirable effects

System organ class	Common ≥1/100 to <1/10	Uncommon ≥1/1 000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very rare <1/10,000	Frequency not known (cannot be estimated from the available data)
Endocrine disorders					Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Metabolism and nutrition disorders		Anorexia, Decreased appetite	Hyperglycaemia, Hypoglycaemia (see section 4.4)		Hypoglycaemic coma (see section 4.4)

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) (see section 4.4), Hallucinations	Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide) (see section 4.4)	Mania, incl. hypomania
Nervous system disorders (*)		Headache, Dizziness, Sleep disorder, Taste disorder	Par- and Dysaesthesia, Hypoaesthesia, Tremor, Seizures (including status epilepticus, see section 4.4), Vertigo	Migraine, Disturbed coordination, Gait disturbance, Olfactory nerve disorder, Intracranial hypertension and pseudotumor cerebri	Peripheral neuropathy and polyneuropathy (see section 4.4)~~Peripheral neuropathy (see section 4.4)~~
Gastrointestinal disorders	Nausea, Diarrhoea	Vomiting, Gastrointestinal and abdominal pain, Dyspepsia, Flatulence	Antibiotic-associated colitis (very rarely with possible fatal outcome) (see section 4.4)	Pancreatitis	
Skin and subcutaneous tissue disorders		Rash, Pruritus, Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae, Erythema multiforme, Erythema nodosum, Stevens-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 ruptures (predominantly Achilles tendon) (see section 4.4), Exacerbation of symptoms of myasthenia gravis (see section 4.4)	

~~**Tissueand bone disorders**~~		~~back pain, chest pain), Arthralgia~~	~~Increased muscle tone and cramping~~	~~Tendinitis Tendon ruptures predominantly Achilles tendon) (see section 4.4), Exacerbation of symptoms of myasthenia gravis (see section 4.4)~~	
Investigations		Increased blood alkaline phosphatase	Prothrombin level abnormal, increased amylase		International normalised ratio increased(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).

**Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.4).

[…]

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 4.4).

4.9 Overdose

[…]

it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Calcium or magnesium containing antacids may theoretically reduce the absorption of ciprofloxacin in overdoses.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

[…]

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	Susceptible	Resistant
Enterobacteriaceae	S ≤0.25 mg/L	R > 0.5 mg/L
Salmonella spp.	S ≤0.06 mg/L	R > 0.06 mg/L
Pseudomonas spp.	S ≤ 0.5 mg/L	R > 0.5 mg/L
Acinetobacter spp.	S ≤ 1 mg/L	R > 1 mg/L
Staphylococcus spp.[1]	S ≤ 1 mg/L	R > 1 mg/L
Haemophilus influenza	S ≤0.06 mg/L	R > 0.06 mg/L
Moraxella catarrhalis	S ≤0.125 mg/L	R > 0.125 mg/L
Neissiria gonorrhoeae	S ≤ 0.03 mg/L	R > 0.06 mg/L
Neissiria meningitidis	S ≤0.03 mg/L	R > 0.03 mg/L
Non-species related breakpoints*	S ≤0.25 mg/L	R > 0.5 mg/L

~~Microorganisms~~	~~Susceptible~~	~~Resistant~~
~~*Enterobacteria*~~	~~S □ 0.5 mg/L~~	~~R > 1 mg/L~~
~~*Pseudomonas*~~	~~S □ 0.5 mg/L~~	~~R > 1 mg/L~~
~~*Acinetobacter*~~	~~S □ 1 mg/L~~	~~R > 1 mg/L~~
~~*Staphylococcus* spp.[1]~~	~~S □ 1 mg/L~~	~~R > 1 mg/L~~
~~*Haemophilus influenza* and *Moraxella catarrhalis*~~	~~S □ 0.5 mg/L~~	~~R > 0.5 mg/L~~
~~*Neissiria gonorrhoeae*~~	~~S □ 0.03 mg/L~~	~~R > 0.06 mg/L~~
~~*Neissiria* meningitidis~~	~~S □ 0.03 mg/L~~	~~R > 0.06 mg/L~~
~~Non-species related breakpoints*~~	~~S □ 0.5 mg/L~~	~~R > 1 mg/L~~

6. PHARMACEUTICAL PARTICULARS

6.5 Nature and contents of container

[…]

The solution is clear and colorless.

העלון לרופא מצורף להודעה זו וכן נשלח לפרסום במאגר התרופות שבאתר האינטרנט של משרד הבריאות.

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בברכה,

מירי חזן

רוקחת ממונה