12/2021

רופא/ה, רוקח/ת נכבד/ה,

ברצוננו להודיעך על עדכון בעלון  של התכשיר :

**GIROFLOX**

**133-31-30984-00**

**צורת מינון:**

SOLUTION FOR INFUSION

**המרכיבים הפעילים:**

**CIPROFLOXACIN 200 MG / 100 ML**

**<u>עדכונים מהותיים בעלון:</u>**

**<u>התוויה עדכנית:</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>עדכון משטר מינון: ראה פרק 4.2 בעלון המצורף</u>**

**<u>עדכונים מהותיים :</u>**

**<u>4.3 Contraindications:</u>**

(…)

- Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

## 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 should only be considered in combination with another appropriate antibacterial agent (e.g. a cephalosporin) unless ciprofloxacin-resistant Neisseria gonorrhoeae can be excluded. (…)

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. (…)

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

(…)

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may as early as 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 increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.

At the first sign of tendinitis (e.g. painful swelling, inflammation), the treatment with ciprofloxacin 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

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 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 first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to suicidal ideations/thoughts culminating in attempted suicide or completed suicide. In the occurrence of such cases, ciprofloxacin should be discontinued.

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 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 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).

(…)

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (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.

(…)

Vitamin K antagonists

Simultaneous administration of ciprofloxacin 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 ciprofloxacin 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, acenocoumarol, phenprocoumon, or fluindione).

(…)

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 AUC and 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 an oral 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 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, 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 is not recommended

## 4.8 Undesirable effects

**Blood and the lymphatic system disorders**

Rare (≥1/10,000 to <1/1,000) - Thrombocytemia

**Endocrine disorders**

Frequency not known (cannot be estimated from the available data)

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

**Metabolism and nutrition disorders**

Uncommon (> 1/1,000 to <1/100) - Decreased appetite

Rare ( ≥1/10,000 to <1/1,000) - Hypoglycaemia (see section 4.4)

Frequency not known (cannot be estimated from the available data)

Hypoglycaemic coma (see section 4.4)

**Psychiatric disorders (*)**

Rare ( ≥1/10,000 to <1/1,000)

potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide) (see section 4.4)

Very rare (<1/10,000) –

(potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed

suicide) (see section 4.4)

Frequency not known (cannot be estimated from the available data) –

Mania, incl. hypomania

**Nervous system disorders (*)**

Rare (≥1/10,000 to <1/1,000)

Seizures (including status epilepticus see section 4.4)

Very rare <1/10,000 - pseudotumor cerebri

Frequency not known (cannot be estimated from the available data) - polyneuropathy

**Eye disorders (*)**

Rare (≥1/10,000 to <1/1,000) – diplopia

**Gastrointestinal disorders**

Rare ( ≥1/10,000 to <1/1,000)

Antibiotic-associated colitis (very rarely with possible fatal outcome) (see section 4.4)

**Skin and subcutaneous tissue disorders**

Frequency not known (cannot be estimated from the available data)

Acute Generalised Exanthematous Pustulosis (AGEP)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

**Investigations**

Frequency not known (cannot be estimated from the available data)

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).

ראה גם עדכון בתכשיר בפרק המיקרוביולוגיה

בוצעו שינויים נוספים לתכשיר:

שינוי יצרן, שינוי בח"ג לא פעילים, שינוי בחיי מדף, שינוי בתנאי איחסון, שינוי בח"א ראשוניים.

בהודעה זו מצוינים שינויים מהותיים והחמרות. בעלון בוצעו שינויים נוספים - יש לעיין בעלון המצורף לפני השימוש בתכשיר .

העלון נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלו מודפס ע"י פניה לבעל הרישום ביואבניר בע"מ , דוד המלך 1 הרצליה פיתוח או בטלפון 09-9544129.

בכבוד רב,

שרית קיראי-קוצ'וק

רוקחת ממונה