SUMMARY OF PRODUCT CHARACTERISTICS

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS AND TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS

- Fluoroquinolones, including CIFLOSIN may cause disabling and irreversible serious adverse reactions, including:
  - Tendinitis and tendon rupture
  - Peripheral neuropathy
  - Central nervous system effects

In patients with any of these reactions, the use of CIFLOSIN should be discontinued immediately and fluoroquinolone use should be avoided.

- Fluoroquinolones, including CIFLOSIN, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid CIFLOSIN use in patients with known history of myasthenia gravis.
- Because fluoroquinolone group medicines, including CIFLOSIN have been associated with serious adverse reactions, reserve for use in patients who have no alternative treatment options for the following indications:
  - Uncomplicated urinary infection
  - Acute bacterial exacerbation of chronic bronchitis

1. NAME OF THE MEDICINAL PRODUCT
CIFLOSIN® 750 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains;
Active substance:
874.5 mg ciprofloxacin hydrochloride monohydrate equivalent to 750 mg ciprofloxacin

Excipients:
For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM
Film coated tablet;
White film coated, slightly convex oblong tablets, embossed DEVA on one side

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Fluoroquinolones, including CIFLOSIN should not be used for acute bacterial exacerbation of chronic bronchitis and uncomplicated urinary infections if alternative treatment options are available due to serious adverse reaction risk. In addition to this susceptibility has to be proven with antibiogram test in urinary infections.

It can be used in these indications when other treatment options have failed.

Consideration should be given to official guidance on the appropriate use of antibacterial

agents. CIFLOSIN should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.

CIFLOSIN 750 mg film coated tablets are indicated for the treatment of the following indications (see Sections 4.4 and 5.1).

Special attention should be paid to available information on resistance to ciprofloxacin before commencing therapy. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Adults:
- Lower respiratory tract infections due to Gram-negative bacteria
  - Exacerbations of chronic obstructive pulmonary disease (see Section 4.4)
  - Broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
  - Pneumonia
- Chronic suppurative otitis media (see Section 4.4)
  - Acute exacerbations of chronic sinusitis, especially when due to Gram-negative bacteria (see Section 4.4)
- Urinary tract infections
  - Uncomplicated urinary tract infections (see Section 4.4)
  - Complicated urinary tract infections (see Section 4.4)
  - Pyelonephritis
- Genital system infections
  - Gonococcal uretritis and cervicitis due to susceptible *Neisseria gonorrhoeae*
  - Epididymo-orchitis including cases due to susceptible *Neisseria gonorrhoeae*
  - Pelvic inflammatory disease including cases due to susceptible *Neisseria gonorrhoeae*
  - Prostatitis
- Infections of the gastrointestinal tract (e.g. travellers' diarrhea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria
- Malignant external otitis (see Section 4.4)
- Infections of the bones and joints
- Over 18 years old prophylaxis of invasive infections due to *Neisseria meningitidis*
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

Children and adolescents:
- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa* (clinical studies were conducted for ages: 5-17 years
- Complicated urinary tract infections and pyelonephritis when other alternatives are not suitable if agent sensitivity is demonstrated (clinical studies were conducted for ages: 1-17 years)
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may be used to treat severe infections in children and adolescents if necessary, when no other treatment options are available.

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (see Sections 4.4 and 5.1).

4.2. Posology and method of administration

Posology:

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to ciprofloxacin of the causative organisms, the renal function of the patient and, in children and adolescents the body weight.

The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.

Treatment of infections due to certain bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci*) may require higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.

Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.

Adults

Indications		**daily dose in mg**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Infections of the lower respiratory tract – Bronchopulmonary infections in cystic fibrous or bronchiectasis – Pneumonia (see Section 4.4)		500 mg to 750 mg twice daily	7 to 14 days
Urinary tract infections (see Section 4.4)	Complicated urinary tract infections	500 mg twice daily	7 days
	Pyelonephritis	500 mg to 750 mg twice daily	at least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
Genital tract infections	Gonococcal uretritis and cervicitis	500 mg as a single dose	1 day (single dose)
	Epididymo-orchitis and pelvic inflammatory diseases	500 mg to 750 mg twice daily	at least 14 days
	Prostatitis	500 mg to 750 mg twice daily	2 to 4 weeks (acute) and 4 to 6 weeks (chronic)
Infections of the gastrointestinal	Diarrhea caused by bacterial pathogens including *Shigella* spp.	500 mg twice daily	1 day

tract and intra-abdominal infections	other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhea		
	Diarrhea caused by *Shigella dysenteriae* type 1	500 mg twice daily	5 days
	Diarrhea caused by *Vibrio cholerae*	500 mg twice daily	3 days
	Typhoid fever	500 mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	500 mg to 750 mg twice daily	5 to 14 days
Skin and soft tissue infections		500 mg to 750 mg twice daily	7 to 14 days
Bone and joint infections		500 mg to 750 mg twice daily	max. of 3 months
Neutropenic patients with fever suspected to be due to a bacterial infection. Ciprofloxacin should be co-administered with appropriate antibacterial agents in accordance to official guidance.		500 mg to 750 mg twice daily	Therapy should be continued over the entire period of neutropenia
Prophylaxis of invasive infections due to *Neisseria meningitidis*		500 mg as a single dose	1 day (single dose)
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.		500 mg twice daily	60 days from the confirmation of *Bacillus anthracis* exposure

Frequency and duration of administration:
See Section 4.2.

Method of administration:
It is administered through oral route. Tablets are to be swallowed whole with some fluid.

It can be taken independent of mealtimes. If taken on an empty stomach, the active substance is absorbed more rapidly. In this case, the tablets should not be taken with dairy products or mineral-fortified drinks (e.g. milk, yoghurt, calcium-fortified orange juice) (see Section 4.5).

Intravenous administration of ciprofloxacin is recommended for patients who cannot take tablets due to the severity of the disease or for other reasons (e.g. if the patient is receiving enteral nutrition). After intravenous administration, treatment can be continued orally.

Additional information for special populations:
Renal impairment:

Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [ml/min/1.73 m^2]	Serum Creatinine [mikromol/L]	Oral Dose [mg]
> 60	< 124	See Usual Dosage.
30-60	124 to 168	250-500 mg every 12 h
< 30	> 169	250-500 mg every 24 h
Patients on hemodialysis	> 169	250-500 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	250-500 mg every 24 h

Dosing in children with impaired renal function has not been studied.

Hepatic impairment:
In patients with impaired liver function no dose adjustment is required.
Dosing in children with impaired hepatic function has not been studied.

Pediatric population:

Indications	daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Cystic fibrosis	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	10 to 14 days
Complicated urinary tract infections and pyelonephritis	10 mg/kg body weight twice daily to 20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	10 to 21 days
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.	10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 500 mg per dose.	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	According to the type of infections

Geriatric population:
Elderly patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.

4.3 Contraindications
- Hypersensitivity to the ciprofloxacin, to other quinolones or to any of the excipients (see Section 6.1).

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

4.4 Special warnings and precautions for use

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older 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, known atherosclerosis).

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

Disabling and potentially irreversible serious adverse reactions including tendinitis and tendon rupture, peripheral neuropathy, and central nervous system effects

Fluoroquinolones, including CIFLOSIN, have been associated with disabling and potentially irreversible serious adverse reactions. Commonly seen adverse reactions musculoskeletal and peripheral nervous system (e.g. tendinitis, tendon rupture, swelling or inflammation of the tendons, tingling or numbness, numbness in arms and legs, muscle pain, muscle weakness, joint pain, swelling in joints) arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (hallucinations, anxiety, depression, suicidality, insomnia, severe headaches, and confusion) (see Section 4.8).

These reactions can occur within hours to weeks after starting CIFLOSIN. Patients of any age or without pre-existing risk factors have experienced these adverse reactions.

Discontinue CIFLOSIN immediately at the first signs or symptoms of any serious adverse reaction. In addition, avoid the use of fluoroquinolones, including CIFLOSIN, in patients who have experienced any of these serious adverse reactions associated with fluoroquinolones.

Acute bacterial exacerbation of chronic bronchitis, acute exacerbations of chronic sinusitis, chronic suppurative otitis media, malignant otitis externa and uncomplicated urinary tract infections

Should only be used in acute bacterial exacerbation of chronic bronchitis, acute exacerbations of chronic sinusitis, chronic suppurative otitis media, malignant otitis externa and uncomplicated urinary tract infections when other treatment options have failed. In addition to this susceptibility has to be proven with antibiogram test in urinary tract infections.

Indications	**daily dose in mg**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Infections of the lower respiratory tract	500 mg to 750 mg twice daily	7 to 14 days

• Exacerbations of chronic obstructive pulmonary disease			
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	500 mg to 750 mg twice daily	7 to 14 days
	Chronic suppurative otitis media	500 mg to 750 mg twice daily	7 to 14 days
	Malignant external otitis	750 mg twice daily	28 days to 3 months
Uncomplicated urinary tract infections		250 mg to 500 mg twice daily	3 days
		In pre-menopausal women, 500 mg single dose may be used	

Severe infections and/or severe infections due to gram-positive or anaerobic bacteria

Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections CIFLOSIN must be co-administered with other appropriate antibacterial agents.

Streptococcal infections (including *Streptococcus pneumoniae*)
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections
Gonococcal uretritis, cervicitis, epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae* isolates. Therefore, CIFLOSIN should be administered for the treatment of gonococcal uretritis or cervicitis only if ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded.

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. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Urinary tract infections
The resistance of *Escherichia coli*, the most commonly associated pathogen in urinary tract infections, to fluoroquinolones varies according to the region of residence. Prescribers are advised to take into account the local prevalence of resistance in *Escherichia coli* to fluoroquinolones in their local area.

The single dose of ciprofloxacin that may be used in uncomplicated urinary tract infections in pre-menopausal women is expected to be associated with lower efficacy than the longer treatment duration. This is all the more to be taken into account as regards the increasing resistance level of *Escherichia coli* to quinolones.

Intra-abdominal infections
There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travelers' diarrhea

The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints
Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Inhalational anthrax
Use in humans is based on *in-vitro* susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax.

Children and adolescents
The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from a randomized double-blind study on ciprofloxacin use in children (ciprofloxacin: n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day +42 of 7.2% and 4.6%. Respectively, an incidence of drug-related arthropathy by 1-year follow-up was 9% and 5.7%. The increase of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue (see Section 4.8).

Broncho-pulmonary infections in cystic fibrosis
Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.

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 microbiological results. Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections
It may be used for 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, CIFLOSIN should be discontinued and an adequate medical treatment is

required.

Musculoskeletal system
CIFLOSIN should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, CIFLOSIN 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 ciprofloxacin.

Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with CIFLOSIN, even within the first 48 hours of treatment. Inflammation and ruptures of tendon may occur even up to several months after discontinuation of ciprofloxacin therapy. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids (see Section 4.8).

At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected leg at rest.

Exacerbation of Myasthenia Gravis:
Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Post-marketing serious adverse reactions, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Avoid fluoroquinolone use in patients with known history of myasthenia gravis (see Section 4.8).

Visual disturbances
If visual impairment begins or if there is any effect on the eyes, an ophthalmologist should be consulted immediately.

Cardiac disorders
It may increase the risk of developing long QT syndrome or Torsades de Pointes when used with drugs that can cause long QT syndrome/Torsades de Pointes. Therefore, it should not be used with such drugs.

Caution should be exercised when using fluoroquinolones, including ciprofloxacin, in patients with known risk factors for QT interval prolongation. For example:
- Congenital long QT syndrome
- Concomitant use of drugs that may cause prolongation of the QT interval (e.g. concomitant use of Class IA or Class III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
- Uncorrected electrolyte imbalance (e.g. Hypokalemia, hypomagnesemia)
- Cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including ciprofloxacin, in these populations (see Sections 4.2, 4.5, 4.8, 4.9).

Hypoglycemia
As with other quinolones, hypoglycemia has been reported most often in diabetic patients,

predominantly in the elderly population. In all diabetic patients, careful monitoring of blood glucose is recommended (see Section 4.8).

Gastrointestinal system
The occurrence of severe and persistent diarrhea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases, CIFLOSIN should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

Photosensitivity
Ciprofloxacin has been shown to cause photosensitivity reactions. Therefore, patients taking CIFLOSIN should not be exposed to intense sunlight or UV rays (see Section 4.8).

Central nervous system (CNS)
Ciprofloxacin like other quinolones are known to trigger seizures or lower the seizure threshold.

Cases of status epilepticus have been reported. CIFLOSIN should be used with caution in patients with central nervous system disorders who are prone to seizures. If seizures occur CIFLOSIN should be discontinued (see Section 4.8).

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. If the patient develops any of these reactions, CIFLOSIN should be discontinued.

Cases of sensory or sensorimotor polyneuropathy resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving ciprofloxacin. CIFLOSIN 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).

Renal and urinary system
Crystalluria related to the use of ciprofloxacin has been reported (see Section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Impaired renal function
Since CIFLOSIN is largely excreted from the kidneys, dose adjustment is needed in patients with impaired renal function to avoid an increase in adverse drug reactions due to accumulation of ciprofloxacin (see Section 4.2).

In elderly patients, caution should be exercised in dose adjustments due to decreased renal function. When renal and hepatic dysfunction occur together, consideration should be given to dose reduction.

Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see Section 4.8). In the event of any signs and symptoms of hepatic disease (anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued (see section 4.8).

Glucose-6-phosphate dehydrogenase deficiency
Hemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of hemolysis should be monitored.

Resistance
During or following a course of treatment with ciprofloxacin 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 inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolized by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine, duloxetine, agomelatin). 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.

Methotrexate
The concomitant use of ciprofloxacin with methotrexate is not recommended (see Section 4.5).

Interaction with tests
The *in-vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

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).

Chelation complex formation
The absorption of ciprofloxacin is reduced when oral ciprofloxacin is taken simultaneously with iron, sucralfate or antacids, strongly buffered drugs (antiretroviral drugs), therapeutic products containing magnesium, aluminum or calcium, and polymeric phosphate binders such as sevelamer and lanthanum carbonate. When needs to use together, CIFLOSIN should be administered either 1-2 hours before or at least 4 hours after these preparations. The restriction does not apply to antacids belonging to the class of H_2 receptor blockers.

Food and dairy products
Dietary calcium as part of a meal does not significantly affect absorption of ciprofloxacin. However, the concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) with ciprofloxacin may reduce the absorption of ciprofloxacin. Therefore, use of CIFLOSIN in this way should be avoided.

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration use with therapeutic products containing probenecid may lead to increase of ciprofloxacin serum concentrations.

Metoclopramide
Metoclopramide (oral) accelerates the absorption of ciprofloxacin and resulting in a shorter time to reach maximum plasma concentrations. However, it has no effect on the bioavailability of ciprofloxacin.

Omeprazole
Concomitant administration of ciprofloxacin and omeprazole containing medicinal products results in a slight reduction of C_{max} and AUC of ciprofloxacin.

Effects of Ciprofloxacin on other medicinal products
Tizanidine
Therapeutic products containing tizanidine should not be administered together with CIFLOSIN (see section 4.3). In a clinical study with healthy subjects, there was 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) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect (see Section 4.4).

Methotrexate
Renal tubular transport of methotrexate may be inhibited by concomitant administration of CIFLOSIN, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use of ciprofloxacin with methotrexate is not recommended (see section 4.4).

Theophylline
Concurrent administration of ciprofloxacin and theophylline-containing therapeutic products can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. If combination use of two therapeutic products is necessary, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary (see Section 4.4).

Other xanthine derivatives
On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

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

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 CIFLOSIN 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 C_{max} 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).

Ropinirole
It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of 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 ciprofloxacin (see Section 4.4).

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

Clozapine
Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with CIFLOSIN are advised (see Section 4.4).

Sildenafil
C_{max} 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 CIFLOSIN concomitantly with sildenafil taking into consideration the risks and the benefits.

Phenytoin
Altered (decreased or increased) serum levels of phenytoin were observed in patients receiving ciprofloxacin and phenytoin simultaneously. Therefore, monitoring of drug levels is recommended.

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 CYP4501A2, similar effects can be expected upon concomitant administration (see Section 4.4).

Zolpidem
Co-administration ciprofloxacin may increase blood levels of zolpidem, concurrent use is not recommended.

4.6 Pregnancy and lactation
General recommendation
Pregnancy category: C

Women of child-bearing potential/Birth control (Contraception)
Sufficient data is not available for use of ciprofloxacin in women with child-bearing potential. As a precaution, an appropriate contraception method is recommended.

Pregnancy
The data that are available on administration of ciprofloxacin to pregnant women indicates no malformation or feto/neonatal toxicity.

In juvenile and animals exposed to quinolones in the prenatal period, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism/ fetus (see Section 5.3).

As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Breast-feeding
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, use of CIFLOSIN during breastfeeding is not recommended (see section 5.3).

Reproductive ability/Fertility
For animal studies, see section 5.3.

4.7 Effects on ability to drive and use machines
Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired (See Section 4.8).

4.8 Undesirable effects
Adverse drug reactions derived from all clinical studies with ciprofloxacin (oral, parenteral) sorted by CIOMS III categories of frequency are listed below (total n= 51621).

Adverse drug reactions frequencies reported with ciprofloxacin are summarized below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Very common (≥1/10); 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); unknown (cannot be estimated from the available data).

The adverse reactions identified only during post marketing surveillance, and for which a frequency could not be estimated, are listed under the title of "unknown".

System Organ Class	Common	Uncommon	Rare	Very Rare	Unknown
Infections and Infestations		Mycotic superinfections			
Blood and Lymphatic System Disorders		Eosinophilia	Leucopenia Anemia Neutropenia Leukocytosis Thrombocytopenia Thrombocythemia	Hemolytic anemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic edema/ angioedema	Anaphylactic reaction, Anaphylactic	

				shock (life-threatening, see section 4.4), Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Decreased appetite and food intake	Hyperglycemia, Hypoglycemia (see section 4.4)		
Psychiatric Disorders		Psychomotor hyperactivity/ agitation	Confusion and disorientation, Anxiety reaction, Abnormal dreams (nightmare), 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 including hypomania
Nervous System Disorders		Headache, Dizziness, Sleep disorders, Taste disorders	Paresthesia, Dysesthesia , Hypoesthesia, Tremor (shake), Seizures (including status epilepticus (see section 4.4), Vertigo	Migraine, Disturbed coordination, Gait disturbance, Olfactory nerve disorders, Intracranial hypertension (pseudotumor cerebry)	Peripheral neuropathy and polyneuropathy (see section 4.4)
Eye Disorders			Visual disturbances (e.g. diplopia)	Visual color distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss/Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia, torsades de pointes (predominantly in patients with risk factors for QT prolongation), ECG QT prolonged (see sections 4.4 and 4.9)
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	
Thoracic and			Dyspnea (including		

Mediastinal Disorders			asthmatic condition)		
Gastrointestinal disorders	Nausea, Diarrhea	Vomiting, Gastrointestinal and abdominal pains, Dyspepsia, Flatulence	Antibiotic associated diarrhea colitis (very rarely fatal)	Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases levels, Increased bilirubin	Hepatic impairment, Cholestatic jaundice Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	
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 generalized exanthematous pustulosis (AGEP) Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal, Connective Tissue and Bone Disorders		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia (joint pain)	Myalgia, Arthritis, Increased muscle tone and cramping	Muscular weakness, Tendinitis, Tendon rupture (predominantly Achilles tendon) (see section 4.4), Exacerbation of symptoms of myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Hematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions		Asthenia, Fever	Edema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Increased amylase		International normalized ratio increased (in patients treated with Vitamin K antagonists)

* These reactions are adverse reactions from post-marketing studies and generally occur in patients with risk

factors for QT prolongation (see section 4.4).

Pediatric patients
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).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose and treatment
An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.

Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and hematuria. Reversible renal toxicity has been reported.
Apart from routine emergency measures, e.g. the administration of medical carbon, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be given plenty of fluids.

Calcium or magnesium containing antacids may reduce the absorption of ciprofloxacin in overdoses.

Only a small quantity of ciprofloxacin (<10%) is eliminated by hemodialysis or peritoneal dialysis. In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antibacterials for systemic use, Fluoroquinolones
ATC code: J01MA02

Mechanism of action
As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

Pharmacokinetic/pharmacodynamic relationship
Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance
In vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV commonly. The results of cross-resistance between ciprofloxacin and other fluoroquinolones are variable. Single mutations may result in reduced susceptibility rather than clinical resistance, but multiple mutations often result in clinical ciprofloxacin resistance and cross-resistance between the quinolone class.

Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in-vitro* mechanisms of resistance are commonly observed in clinical isolates. Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin.

Plasmid-mediated resistance encoded by *qnr*-genes has been reported.

Spectrum of antibacterial activity
Minimum concentration levels (breakpoints) at which bacteria are susceptible or resistant distinguish susceptible strains from intermediately susceptible strains and intermediately susceptible from resistant strains:

EUCAST recommendations

Microorganisms	Susceptible	Resistant
Enterobacteriae	Susceptible ≤ 0.5 mg/L	Resistant > 1 mg/L
Pseudomonas species	Susceptible ≤ 0.5 mg/L	Resistant > 1 mg/L
Acinetobacter species	Susceptible ≤ 1 mg/L	Resistant > 1 mg/L
Staphylococcus species[1]	Susceptible ≤ 1 mg/L	Resistant > 1 mg/L
Haemophilus influenzae and *Moraxella catarrhalis*	Susceptible ≤ 0.5 mg/L	Resistant > 0.5 mg/L
Neisseria gonorrhoeae	Susceptible ≤ 0.03 mg/L	Resistant > 0.06 mg/L
Neisseria meningitidis	Susceptible ≤ 0.03 mg/L	Resistant > 0.06 mg/L
Non-species-related breakpoints*	Susceptible ≤ 0.5 mg/L	Resistant > 1 mg/L
1 *Staphylococcus* species- breakpoints for ciprofloxacin relate to high dose therapy. * Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species.		

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent, in at least some types of infections, is questionable.

The following bacterial gens and species have been shown to be commonly susceptible to ciprofloxacin *in vitro*:

Aerobic Gram-positive microorganisms
Bacillus anthracis (1)

Aerobic Gram-negative microorganisms
Aeromonas spp.
Brucella spp.
Citrobacter koseri
Francisella tularensis
Haemophilus ducreyi
*Haemophilius influenza**
Legionella spp.
*Moraxella catarrhalis**
Neisseria meningitidis
Pasteurella spp.
Salmonella spp.*
Shigella spp.*
Vibrio spp.
Yersinia pestis

Anaerobic microorganisms
Mobiluncus

Other microorganisms
Chlamydia trachomatis ($)
Chlamydia pneumoniae ($)
Mycoplasma hominis ($)
Mycoplasma pneumoniae ($)

Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Enterococcus faecalis ($)
Staphylococcus spp. (2)*

Aerobic Gram-negative microorganisms

Acinetobacter baumanni+	*Klebsiella pneumoniae**
*Burkholderia cepacia+**	*Morganella morganii**
*Camplybacter spp. +**	*Neisseria gonorrhoeae**
*Citrobacter freundii**	*Proteus mirabilis**
Enterobacter aerogenes	*Proteus vulgaris**
*Enterobacter cloacae**	*Providencia spp.*
*Escherichia coli**	*Pseudomonas aeruginosa**
Klebsiella oxytoca	*Pseudomonas fluorescens*
*Serratia marcescens**	

Anaerobic microorganisms
Peptostreptococcus spp.
Propionibacterium acnes

The following microorganisms are considered inherently resistant to ciprofloxacin:

Aerobic Gram-positive microorganisms
Actinomyces
Enteroccus faecium
Listeria monocytogenes

Aerobic Gram-negative microorganisms
Stenotrophomonas maltophilia

Anaerobic microorganisms
Excepted as listed above

Other microorganisms
Mycoplasma genitalium
Ureaplasma urealitycum

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

+ Resistance rate ≥ 50% in one or more EU countries
($)Natural intermediate susceptibility in the absence of acquired mechanism of resistance
(1) Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in-vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and/or international consensus documents regarding treatment of anthrax.
(2) Methicillin-resistant *S. aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later.
Single doses of 100-750 mg produced dose-dependent maximum serum concentrations (C_{max}) between 0.56 and 3.7 mg/L. Serum concentrations increase proportionately with doses up to 1000 mg. The absolute bioavailability is approximately 70-80%.
A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration-time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours.

Distribution

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentration exceeds the plasma concentration plasma concentration.

Biotransformation

Low concentrations of 4 metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display *in-vitro* antimicrobial activity but to a lower degree than the parent compound.

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, fecally. The serum elimination half-life in subjects with normal renal function is approximately 4-7 hours.

Excretion of ciprofloxacin dosage (% of dose)	
	Oral administration

	Urine	Feces
Ciprofloxacin	44.7	25.0
Metabolites (M_1-M_4)	11.3	7.5

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half-lives of ciprofloxacin of up to 12 h.
Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Pediatric patients
The pharmacokinetic data in pediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.8-32.0 mg*h/L) and 16.5 mg*h/L (range 11.0-23.8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of pediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

5.3 Preclinical safety data
Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction. Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was similiar to that of other gyrase inhibitors.

Articular tolerability studies:
As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in immature animals.

The extent of the cartilage damage varies according to age, species and dose. the damage can be reduced by not placing too much stress on the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Uncoated tablet:
Microcrystalline cellulose
Maize starch
Crospovidone CL

Colloidal silicon dioxide
Magnesium stearate

Film coating material:
Opadry OY-D-7233 white
- Hydroxypropyl methyl cellulose
- Titanium dioxide
- Talc
- Polyethylene glycol
- Sodium lauryl sulphate

6.2 Incompatibilities
Not indicated.

6.3 Shelf life
60 months

6.4 Special precautions for storage
Should be stored at room temperature below 25°C.

6.5 Nature and contents of packaging
Structure of the packaging material:
Blister with transparent PVDC foil one side and printed aluminum foil on the other.
Each cardboard box contains blister of 10 tablets or 14 tablets.

6.6 Special precautions for disposal and other handling
Any unused material should be disposed according to local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER
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