SUMMARY OF PRODUCT CHARACTERISTICS

1 Name of the medicinal product

Tasaroxin IV 2mg/ml solution for infusion

2 Qualitative and quantitative composition

1 ml solution for infusion contains Ciprofloxacin lactate equivalent to 2mg ciprofloxacin. Each bag with 50ml contains 100mg ciprofloxacin. Each bag with 100ml contains 200mg ciprofloxacin.
Excipient with known effect: 15.4 mmol (354 mg) sodium per 100 ml of solution for infusion.

For the full list of excipients, see section 6.1.

3 Pharmaceutical form

Solution for infusion
Clear, colourless to yellow solution.

4 Clinical particulars

4.1 Therapeutic indications

Ciprofloxacin 2 mg/ml solution for infusion is indicated for the treatment of the following infections (see sections 4.4 and 5.1). Special attention should be paid to available information on resistance to ciprofloxacin before commencing therapy.

Adults

- Lower respiratory tract infections due to Gram-negative bacteria
  - exacerbations of chronic obstructive pulmonary disease. In exacerbations of chronic obstructive pulmonary disease Ciprofloxacin should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.
  - broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
  - pneumonia
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Acute pyelonephritis
- Bacterial prostatitis
- Genital tract infections
  - epididymo-orchitis including cases due to susceptible *Neisseria gonorrhoeae*
  - pelvic inflammatory disease including cases due to susceptible *Neisseria gonorrhoeae*
- Infections of the gastro-intestinal tract (e.g., travellers` diarrhoea)
- Intra-abdominal infections
- Complicated skin and skin structure infections/complicated skin and soft tissue infections
- Malignant external otitis
- Infections of the bones and joints
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Children and adolescents

- Broncho-pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis
- Complicated urinary tract infections and acute pyelonephritis

• Inhalation anthrax (post-exposure prophylaxis and curative treatment)
Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

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

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 organism(s), 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. After intravenous initiation of treatment, the treatment can be switched to oral treatment with tablet or suspension if clinically indicated at the discretion of the physician. IV treatment should be followed by oral route as soon as possible.

In severe cases or if the patient is unable to take tablets (e.g., patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

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**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
Infections of the lower respiratory tract		400mg twice daily to 400mg three times a day	7 to 14 days
Infections of the upper respiratory tract Ear infections	Acute exacerbation of chronic sinusitis	400mg twice daily to 400mg three times a day	7 to 14 days

Adults

Indications		Daily dose	Total duration of treatment (including switch to oral therapy as soon as possible)
	Chronic suppurative otitis media	400mg twice daily to 400mg three times a day	7 to 14 days
	Malignant external otitis	400mg three times a day	28 days up to 3 months
Urinary tract infections (see section 4.4)	Acute pyelonephritis	400mg twice daily to 400mg three times a day	7 to 21 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Bacterial prostatitis	400mg twice daily to 400mg three times a day	2 to 4 weeks (acute)
Genital tract infections	Epididymo-orchitis and pelvic inflammatory diseases	400mg twice daily to 400mg three times a day	at least 14 days
Infections of the gastro-intestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens including *Shigella* spp. other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhoea	400mg twice daily	1 day
	Diarrhoea caused by *Shigella dysenteriae* type 1	400mg twice daily	5 days
	Diarrhoea caused by *Vibrio cholerae*	400mg twice daily	3 days
	Typhoid fever	400mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	400mg twice daily to 400mg three times a day	5 to 14 days
Complicated skin and structure infections/complicated skin and soft tissue infections		400mg twice daily to 400mg three times a day	7 to 14 days
Infections of the bones and joints		400mg twice daily to 400mg three times a day	maximum of 3 months

Adults		
Indications	**Daily dose**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
Management of neutropenic patients with fever Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.	400mg twice daily to 400mg three times a day	Therapy should be continued over the entire period of neutropenia
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons requiring parenteral treatment Drug administration should begin as soon as possible after suspected or confirmed exposure.	400mg twice daily	60 days from the confirmation of *Bacillus anthracis* exposure

Paediatric population		
Indications	**Daily dose**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
Broncho-pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis	10mg/kg body weight three times a day with a maximum of 400mg per dose.	10 to 14 days
Complicated urinary tract infections and acute pyelonephritis	6mg/kg body weight three times a day to 10mg/kg body weight three times a day with a maximum of 400mg per dose.	10 to 21 days
Inhalation anthrax post-exposure curative treatment for persons requiring parenteral treatment Drug administration should begin as soon as possible after suspected or confirmed exposure.	10mg/kg body weight twice daily to 15mg/kg body weight twice daily with a maximum of 400mg per dose.	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	10mg/kg body weight three times a day with a maximum of 400mg per dose.	According to the type of infections.

Elderly patients

Elderly patients should receive a dose selected according to the severity of the infection and the patient`s creatinine clearance.

Patients with renal and hepatic impairment

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

Creatinine Clearance [ml/min/1.73 m^2]	Serum Creatinine [µmol/l]	Intravenous Dose [mg]
> 60	< 124	See usual dosage.
30 – 60	124 to 168	200 – 400 mg every 12 h
< 30	> 169	200 – 400 mg every 24 h
Patients on haemodialysis	> 169	200 – 400 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	200 – 400 mg every 24 h

In patients with impaired liver function no dose adjustment is required.
Dosing in children with impaired renal and/or hepatic function has not been studied.

Method of administration
Ciprofloxacin should be checked visually prior to use. It must not be used if cloudy. Ciprofloxacin should be administered by intravenous infusion.
For children, the infusion duration is 60 minutes.
In adult patients, infusion time is 60 minutes for 400mg Ciprofloxacin and 30 minutes for 200mg Ciprofloxacin.
Slow infusion into a large vein will minimize patient discomfort and reduce the risk of venous irritation.
The infusion solution can be infused either directly or after mixing with other compatible infusion solutions (see section 6.6).

4.3 Contraindications

• Hypersensitivity to the active substance, to other quinolones or to any of the excipients listen in section 6.1.
• 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 also section 4.3).

Severe infections and mixed infections with Gram-positive and anaerobic pathogens
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, ciprofloxacin 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
Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. 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
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.

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

Travellers' diarrhoea
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.

Paediatric population
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 randomised 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 9.0% 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).

Prolonged, disabling and potentially irreversible serious adverse drug reactions

or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

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 acute 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.

Tendinitis and tendon rupture
Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur 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. 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 (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

Myasthenia gravis
Ciprofloxacin should be used with caution in patients with myasthenia gravis (see section 4.8).

Photosensitivity
Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Central Nervous System
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). Psychiatric reactions may occur even after the 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.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, 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)

Cardiac disorders

Caution should be taken when using fluoroquinolones, including ciprofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:

- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- 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 section 4.2 Elderly, section 4.5, section 4.8, section 4.9).

Aortic aneurysm and dissection

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.

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported (see section 4.8), usually in 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.

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

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 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.

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 (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.

Glucose-6-phosphate dehydrogenase deficiency
Haemolytic reactions have been reported with 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 haemolysis 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 metabolised by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine, duloxetine, agomelatine). Co-administration of ciprofloxacin and tizanidine is contra-indicated. 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).

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.

Injection Site Reaction
Local intravenous site reactions have been reported with the intravenous administration of ciprofloxacin. These reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

NaCl Load
In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.), the additional sodium load should be taken into account (for sodium chloride content, see section 2).

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

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 the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4).

Probenecid
Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

Effects of ciprofloxacin on other medicinal products:
Tizanidine
Tizanidine must not be administered together with ciprofloxacin (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.

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).

Theophylline
Concurrent administration of ciprofloxacin and theophylline 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. During the combination, 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.

Phenytoin
Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

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 anticoagulant 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 normalized ratio) is difficult to assess. The INR should be monitored frequently during and shortly after coadministration 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 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, 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.

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 ciprofloxacin 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 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 ('Cytochrome P450' in section 'Special warnings and precautions for use).

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

4.6 Fertility, pregnancy and lactation

Pregnancy
The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, 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 / foetus (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Lactation
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

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.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea, vomiting, transient increase in transaminases, rash, and injection and infusion site reactions.
ADRs derived from clinical studies and post-marketing surveillance with ciprofloxacin (oral, intravenous and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

Term	Frequency of occurrence
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)
Not known	(cannot be estimated from the available data)

System Organ Class	Frequency	Undesirable effects
Infections and infestations	Uncommon	Mycotic superinfections
Blood and lymphatic system disorders	Uncommon	Eosinophilia
	Rare	Leukopenia, Anaemia, Neutropenia, Leukocytosis, Thrombocytopenia Thrombocytaemia
	Very rare	Haemolytic anaemia, Agranulocytosis, Pancytopenia (life-threatening), Bone marrow depression (life-threatening)
Immune system disorders	Rare	Allergic reaction, Allergic oedema / angioedema
	Very rare	Anaphylactic reaction, Anaphylactic shock (life-threatening) (see section 4.4), Serum sickness-like reaction
Endocrine disorders	Not known	Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Metabolism and nutrition disorders	Uncommon	Decreased appetite
	Rare	Hyperglycaemia, Hypoglycaemia (see section 4.4)
	Not known	Hypoglycaemic coma (see section 4.4)
Psychiatric disorders*	Uncommon	Psychomotor hyperactivity / agitation
	Rare	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
	Very rare	Psychotic reactions (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide) (see section 4.4)
	Not known	Mania, hypomania
Nervous system disorders*	Uncommon	Headache, Dizziness, Sleep disorders, Taste disorders
	Rare	Par- and dysaesthesia, Hypoaesthesia, Tremor, Seizures (incl. status epilepticus see section 4.4), Vertigo
	Very rare	Migraine disturbed coordination, Gait disturbance, Olfactory nerve disorders, Intracranial hypertension and pseudotumor cerebri

	Not known	Peripheral neuropathy (see section 4.4)
Eye disorders*	Rare	Visual disturbances (e.g. diplopia)
	Very rare	Visual colour distortions

System Organ Class	**Frequency**	**Undesirable effects**
Ear and labyrinth disorders*	Rare	Tinnitus, Hearing loss / hearing impaired
Cardiac disorders	Rare	Tachycardia
	Not known	Ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged (see section 4.4 and 4.9)
Vascular disorders	Rare	Vasodilatation, Hypotension, Syncope
	Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	Rare	Dyspnoea (including asthmatic condition)
Gastrointestinal disorders	Common	Nausea, Diarrhoea
	Uncommon	Vomiting, Gastrointestinal and abdominal pains, Dyspepsia, Flatulence
	Rare	Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)
	Very rare	Pancreatitis
Hepatobiliary disorders	Uncommon	Increase in transaminases, Increased bilirubin
	Rare	Hepatic impairment, Cholestatic icterus, Hepatitis
	Very rare	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)
Skin and subcutaneous tissue disorders	Uncommon	Rash, Pruritus, Urticaria
	Rare	Photosensitivity reactions (see section 4.4)
	Very rare	Petechia, Erythema multiforme, Erythema nodosum, Stevens-Johnson syndrome (potentially life-threatening), Toxic epidermal necrolysis (potentially life-threatening)
	Not known	Acute generalised exanthematous pustulosis (AGEP), DRESS
Musculoskeletal, connective tissue and bone disorders*	Uncommon	Musculoskeletal pain (e.g. extremity pain, back pain, chest pain), Arthralgia
	Rare	Myalgia, Arthritis, Increased muscle tone and cramping

	Very rare	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	Uncommon	Renal impairment
	Rare	Renal failure, Haematuria, Crystalluria (see section 4.4), Tubulointerstitial nephritis

System Organ Class	**Frequency**	**Undesirable effects**
General disorders and administration site conditions*	Common	Injection and infusion site reactions (only intravenous administration)
	Uncommon	Asthenia, Fever
	Rare	Oedema, Sweating (hyperhidrosis)
Investigations	Uncommon	Increase in blood alkaline phosphatase
	Rare	Increase amylase
	Not known	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).

The following undesirable effects have a higher frequency category in the subgroups of patients receiving intravenous or sequential (intravenous to oral) treatment:

Common	Vomiting, Transient increase in transaminases, Rash
Uncommon	Thrombocytopenia, Thrombocytaemia, Confusion and disorientation Hallucinations, Par- and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Cholestatic icterus, Renal failure, Oedema
Rare	Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Olfactory nerve disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture

Paediatric population
The incidence of arthropathy, 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 Authorisation 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 Pharmacovigilance Electronic Reporting System (PvERS)
https://pv.pharmacyboardkenya.org/

4.9 Overdose

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 haematuria. Reversible renal toxicity has been reported.

Apart from routine emergency measures, e.g., ventricular emptying followed by medical carbon, 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.

Only a small quantity of ciprofloxacin (< 10%) is eliminated by haemodialysis 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: Fluoroquinolones, ATC code: J01MA02

Mechanism of action

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

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. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the 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
Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:
EUCAST Recommendations

Microorganisms	Susceptible	Resistant
Enterobacteriaceae	S ≤ 0.5 mg/l	R > 1 mg/l
Pseudomonas spp.	S ≤ 0.5 mg/l	R > 1 mg/l
Acinetobacter spp.	S ≤ 1 mg/l	R > 1 mg/l
Staphylococcus spp.[1]	S ≤ 1 mg/l	R > 1 mg/l
Haemophilus influenzae and Moraxella catarrhalis	S ≤ 0.5 mg/l	R > 0.5 mg/l

Microorganisms	Susceptible	Resistant
Neisseria gonorrhoeae	S ≤ 0.03 mg/l	R > 0.06 mg/l
Neisseria meningitidis	S ≤ 0.03 mg/l	R > 0.06 mg/l
Non-species-related breakpoints*	S ≤ 0.5 mg/l	R > 1 mg/l

[1] *Staphylococcus* spp. - 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. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

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.

Groupings of relevant species according to ciprofloxacin susceptibility (for *Streptococcus* species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES	
Aerobic Gram-positive micro-organisms	
Bacillus anthracis (1)	
Aerobic Gram-negative micro-organisms	
Aeromonas spp.	*Moraxella catarrhalis**
Brucella spp.	*Neisseria meningitidis*
Citrobacter koseri	*Pasteurella* spp.
Francisella tularensis	*Salmonella* spp.*
Haemophilus ducreyi	*Shigella* spp. *
*Haemophilus influenzae**	*Vibrio* spp.
Legionella spp.	*Yersinia pestis*

Anaerobic micro-organisms	
Mobiluncus	
Other micro-organisms	
Chlamydia trachomatis (◆)	*Mycoplasma hominis* (◆)
Chlamydia pneumoniae (◆)	*Mycoplasma pneumoniae* (◆)
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM	
Aerobic Gram-positive micro-organisms	
Enterococcus faecalis (◆)	*Staphylococcus* spp. *(2)
Aerobic Gram-negative micro-organisms	
Acinetobacter baumannii+	*Morganella morganii**
Burkholderia cepacia +*	*Neisseria gonorrhoeae**
Campylobacter spp.+*	*Proteus mirabilis**
*Citrobacter freundii**	*Proteus vulgaris**
Enterobacter aerogenes	*Providencia* spp.
*Enterobacter cloacae **	*Pseudomonas aeruginosa**
*Escherichia coli**	*Pseudomonas fluorescens*
Klebsiella oxytoca	*Serratia marcescens**
*Klebsiella pneumoniae**	
Anaerobic micro-organisms	
Peptostreptococcus spp.	*Propionibacterium acnes*
INHERENTLY RESISTANT ORGANISMS	
Aerobic Gram-positive micro-organisms	
Actinomyces	*Listeria monocytogenes*
Enteroccus faecium	
Aerobic Gram-negative micro-organisms	
Stenotrophomonas maltophilia	
Anaerobic micro-organisms	
Excepted as listed above	
Other micro-organisms	
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 an intravenous infusion of ciprofloxacin the mean maximum serum concentrations were achieved at the end of infusion. Pharmacokinetics of ciprofloxacin were linear over the dose range up to 400 mg administered intravenously.

Comparison of the pharmacokinetic parameters for a twice a day and three times a day intravenous dose regimen indicated no evidence of drug accumulation for ciprofloxacin and its metabolites.

A 60-minute intravenous infusion of 200 mg ciprofloxacin or the oral administration of 250 mg ciprofloxacin, both given every 12 hours, produced an equivalent area under the serum concentration time curve (AUC).

A 60-minute intravenous infusion of 400 mg ciprofloxacin every 12 hours was bioequivalent to a 500 mg oral dose every 12 hours with regard to AUC.

The 400 mg intravenous dose administered over 60 minutes every 12 hours resulted in a C_{max} similar to that observed with a 750 mg oral dose.

A 60-minute infusion of 400 mg ciprofloxacin every 8 hours is equivalent with respect to AUC to 750 mg oral regimen given 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 concentrations exceeding those of plasma concentrations are reached.

Biotransformation
Low concentrations of four 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, faecally.

Excretion of ciprofloxacin (% of dose)		
	Intravenous administration	
	Urine	**Faeces**
Ciprofloxacin	61.5	15.2
Metabolites (M_1 – M_4)	9.5	2.6

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.

Paediatric population
The pharmacokinetic data in paediatric 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 (10mg/kg three times daily) was observed.
In 10 children with severe sepsis C_{max} was 6.1 mg/l (range 4.6-8.3mg/l) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2mg/l (range 4.7-11.8mg/l) for children between 1 and 5 years of age. The AUC values were 17.4 mg • h/l (range 11.8-32.0mg • 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 paediatric 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 hazard 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 comparable to that of other gyrase inhibitors.

Articular tolerability
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 taking the weight off 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

Lactic acid
Sodium
chloride
Sodium hydroxide & Hydrochloric acid for pH
adjustment Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

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

Incompatibility appears with all infusion solutions/drugs that are physically or chemically unstable at the pH of the solutions (e.g. penicillins, heparin solutions), especially in combination with solutions adjusted to an alkaline pH (pH of ciprofloxacin solutions: 3.9 – 4.5).

6.3 Shelf life

IV bags: 2 years

6.4 Special precautions for storage

Do not refrigerate or freeze.
Keep the bag in the outer carton/aluminium overpouch until time of use in order to protect from light.

6.5 Nature and contents of container

IV bags:
Polyolefin/ Styrene-block co-polymer-based film bag, provided with a Single Function Connector System (SFC) assembly, comprising of polypropylene port and a polypropylene cap assembled with rubber disc. Sealed with triple laminated over pouch.

Pack size: 50ml or 100ml bags (100mg or 200mg ciprofloxacin) in packs of 1 or 10 bags. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solution should be visually inspected prior to use and only clear solutions, without particles, should be used.
The infusion contains no preservatives. For single use only. Any remaining solution and vials and/or bags should be adequately disposed of, in accordance with local

requirements.

Ciprofloxacin is compatible with physiological sodium chloride solution, Ringer's solution, Ringer's lactate solution, 50 mg/ml (5 %) or 100 mg/ml (10 %) glucose solution and 50 mg/ml (5 %) glucose solution with
2.25 mg/ml (0.225 %) or 4.5 mg/ml (0.45 %) sodium chloride solution and 10% fructose solution. Compatibility with these solutions has been proven in ciprofloxacin concentrations of 1 mg/ml. Chemical and physical in-use stability has been demonstrated immediately after dilution, after 24 hours at 2-8°C and after 24 hours at room temperature. Unless compatibility is proven, the solution for infusion should always be administered separately.

The diluted solutions should be inspected visually for particulate matter and discoloration prior to administration. Only clear and colourless solutions should be used.

Handling IV bags:
Do not remove unit from overwrap until ready for use. The overwrap is a moisture barrier. The inner bag maintains the sterility of the product.

To open, tear overwrap down side at slit and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually. After removing overwrap, check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution as sterility may be impaired.

CAUTION: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed.

7 Marketing authorisation holder

Tasa Pharma Limited Unit C1-C3
Kay complex Nairobi Kenya

8. Market authorization number
H2022/CTD9907/21118

9. Date of registration/renewal of registration
15/12/2022

10. Date of revision of the text
22/08/2026