Summary of Product Characteristics

NOVIDAT® Tablets

NOVIDAT® Oral Suspension

NOVIDAT® Injection/ NOVIDAT® DS Injection

NOVIDAT®
(Ciprofloxacin HCl)

1. NAME OF THE PRODUCT
NOVIDAT® (Ciprofloxacin HCl) 250mg Tablets
NOVIDAT® (Ciprofloxacin HCl) 500mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
NOVIDAT® 250mg Tablets
Each film coated tablet contains:
Ciprofloxacin Hydrochloride USP equivalent to Ciprofloxacin.....250mg

NOVIDAT® 500mg Tablets
Each film coated tablet contains:
Ciprofloxacin Hydrochloride USP equivalent to Ciprofloxacin.....500mg

3. PHARMACEUTICAL FORM
Film-coated tablet

Appearance:
NOVIDAT® 250mg Tablets: White to off-white color capsular film coated tablets. Engraved "**NOVIDAT**" on both sides.
NOVIDAT® 500mg Tablets: White to off-white color capsular film coated tablets. Engraved "**NOVIDAT**" on both sides.

4. CLINICAL PARTICULARS
4.1. THERAPEUTIC INDICATIONS:
Because of the risk of prolonged, disabling and potentially irreversible serious adverse drug reactions this product must only be prescribed when other antibiotics that are commonly recommended for the infection are inappropriate. This applies to all indications listed below. Situations where other antibiotics are considered to be inappropriate are where:

- There is resistance to other first-line antibiotics recommended for the infection.
- Other first-line antibiotics are contraindicated in an individual patient.
- Other first-line antibiotics have caused side effects requiring treatment to be stopped.
- Treatment with other first-line antibiotics has failed.

NOVIDAT® 250mg film-coated tablets are indicated for the treatment of the following infections. 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. In exacerbation 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.
- Urinary tract infections
  - Uncomplicated acute cystitis. In uncomplicated acute cystitis 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.
  - Acute pyelonephritis.
  - Complicated urinary tract infections.
  - Bacterial prostatitis
- Genital tract 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*
- Infections of the gastro-intestinal tract (e.g. travelers' diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria
- Malignant external otitis
- Infections of the bones and joints
- Prophylaxis of invasive infections due to *Neisseria meningitides*
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

NOVIDAT® 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 due to *Pseudomonas aeruginosa* in patients with cystic fibrosis
- Complicated urinary tract infections and pyelonephritis

- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when 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.

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. 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		500mg twice daily to 750mg twice daily	7 to 14 days
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	500mg twice daily to 750mg twice daily	7 to 14 days
	Chronic suppurative otitis media	500mg twice daily to 750mg twice daily	7 to 14 days
	Malignant external otitis	750mg twice daily	28 days up to 3 months
	Uncomplicated acute cystitis	250mg twice daily to 500mg twice daily	3 days

Urinary tract infections		In pre-menopausal women, 500mg single dose may be used	
	Complicated cystitis, Acute pyelonephritis	500mg twice daily	7 days
	Complicated pyelonephritis	500mg twice daily to 750mg twice daily	At least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Bacterial Prostatitis	500mg twice daily to 750mg twice daily	2 to 4 weeks (acute) to 4 to 6 weeks (chronic)
Genital tract infections	Gonococcal uretritis and cervicitis due to susceptible *Neisseria gonorrhoeae*	500mg as a single dose	1 day (single dose)
	Epididymo-orchitis and pelvic inflammatory diseases including cases due to susceptible *Neisseria gonorrhoeae*	500mg twice daily to 750mg twice daily	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 traveler's diarrhoea	500mg twice daily	1 day
	Diarrhoea caused by *Shigella dysenteriae* type 1	500mg twice daily	5 days
	Diarrhoea caused by *Vibrio cholerae*	500mg twice daily	3 days

	Typhoid fever	500mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	500mg twice daily to 750mg twice daily	5 to 14 days
Infections of the skin and soft tissue caused by Gram-negative bacteria		500mg twice daily to 750mg twice daily	7 to 14 days
Bone and joint infections		500mg twice daily to 750mg twice daily	Max. of 3 months
Neutropaenic patients with fever that is suspected to be due to a bacterial infection. Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance		500mg twice daily to 750mg twice daily	Therapy should be continued over the entire period of neutropaenia
Prophylaxis of invasive infections due to *Neisseria meningitidis*		500mg 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.		500mg twice daily	60 days from the confirmation of *Bacillus anthracis* exposure

Paediatric population:

Indications	**Daily dose in mg**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Cystic fibrosis	20mg/kg body weight twice daily with a maximum of 750mg per dose	10 to 14 days

Complicated urinary tract infections and pyelonephritis	10mg/kg body weight twice daily to 20mg/kg body weight twice daily with a maximum of 750mg 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.	10mg/kg body weight twice daily to 15mg/kg body weight twice daily with a maximum of 500mg per dose	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	20mg/kg body weight twice daily with a maximum of 750mg 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/1.73m^2]	**Serum Creatinine [µmol/L]**	**Oral Dose [mg]**
>60	<124	See Usual Dosage
30-60	124 to 168	250-500mg every 12h
<30	>169	250-500mg every 24h
Patients on haemodialysis	>169	250-500mg every 24h (after dialysis)
Patients on peritoneal dialysis	>169	250-500mg every 24h

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:

- Tablets are to be swallowed unchewed with fluid. They can be taken independent of mealtimes. If taken on an empty stomach, the active substance is absorbed more rapidly. Ciprofloxacin tablets should not be taken with dairy products (e.g. Milk, yoghurt) or mineral-fortified fruit juice (e.g. calcium-fortified orange juice).
- 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.

4.3. CONTRAINDICATIONS:

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients.
- Concomitant administration of ciprofloxacin and tizanidine.

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. Treatment of these patients with Ciprofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.

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: Gonococcal urethritis, cervicitis, epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae* isolates. Therefore, Ciprofloxacin 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: Resistance to fluoroquinolones of *Escherichia coli* – the most common pathogen involved in urinary tract infections. Prescribers are advised to take into account the local prevalence of resistance in *Escherichia coli* to fluoroquinolones. The single dose of ciprofloxacin that may be used in

uncomplicated cystitis in pre-menopausal women is expected to be associated with lower efficacy than with 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' 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. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue.

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 the results of the microbiological documentation.

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 and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

Prolonged, disabling and potentially irreversible serious adverse drug reactions: Cases of prolonged (continuing for months or years), disabling and potentially irreversible serious adverse drug reactions affecting different,

sometimes multiple, body systems (including musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. Ciprofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice, so that symptoms can be appropriately investigated and to avoid further exposure which could potentially worsen adverse reactions.

Tendinitis and tendon rupture: Ciprofloxacin 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, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the events of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin. 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 sold organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided. At any sign of tendinitis (e.g. painful swelling, inflammation), the treatment with ciprofloxacin treatment should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilization). Corticosteroids should not be used if signs of tendinopathy occur.

Patients with myasthenia gravis: Ciprofloxacin should be used with caution in patients with myasthenia gravis, because symptoms can be exacerbated.

Aortic aneurysm and dissection, and heart valve regurgitation/ incompetence: Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/ incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones. 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 congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection or heart valves disease, or in presence of other risk factors or conditions predisposing.

- For both aortic aneurysm and dissection and heart valve regurgitation/ incompetence (e.g. connective tissue disorders such as Marfan syndrome

or Ehlers-Danlos syndrome, Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis or additionally.

- For aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or additionally.
- For heart valve regurgitation/incompetence (e.g. infective endocarditis).

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

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

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.

Seizures: Ciprofloxacin like other quinolones is 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.

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.

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

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-arrhythmic, 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.

Dysglycaemia: As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported, 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 (lifethreatening with possible fatal outcome), requiring immediate treatment. 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. 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 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. 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 metabolized by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine, duloxetine, agomelatine). Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for

clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary. Co-administration of ciprofloxacin and tizanidine is contraindicated.

Methotrexate: The concomitant use of ciprofloxacin with methotrexate is not recommended.

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.

Important information regarding the ingredients of this tablet: Sodium: This medicine contains less than 1mmol sodium (23mg) per tablet, that is to say essentially 'sodium-free'.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

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).

Chelation Complex Formation: The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer or lanthanum carbonate), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin. Consequently, ciprofloxacin 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. However, the concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) with ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced.

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

Metoclopramide: Metoclopramide accelerates the absorption of ciprofloxacin (oral) resulting in a shorter time to reach maximum plasma concentrations. No effect was seen 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: Tizanidine must not be administered together with ciprofloxacin. There is 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.

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.

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.

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

Vitamin K antagonists: Simultaneous administration of ciprofloxacin with a vitamin K antagonist may augment its anti-coagulant effects. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalized ratio) is difficult to assess. The INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with a vitamin K antagonist (e.g. warfarin, acenocoumarol, phenprocoumon or fluindione).

Duloxetine: 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.

Ropinirole: 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 coadministration with ciprofloxacin.

Lidocaine: 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 is well tolerated, a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.

Clozapine: Following concomitant administration of 250mg 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.

Sildenafil: Caution should be used prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.

Agomelatine: 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

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

4.6. FERTILITY, PREGNANCY AND LACTATION:

Fertility: Not known.

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

Adverse reactions are ranked by system organ class and then by frequency with the most frequent first, using the following convention:

Common (≥ 1/100 to <1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥1/10,000 to <1/1000); Very Rare (1/10,000); Not known (cannot be estimated from the available data)

Infections and Infestations:

Uncommon: Mycotic super infections.

Blood and lymphatic system disorders:
Uncommon: Eosinophilia.
Rare: Leukopaenia, anaemia, neutropaenia, leukocytosis, thrombocytopaenia, thrombocytaemia.
Very Rare: Haemolytic anaemia, agranulocytosis pancytopaenia (life-threatening), bone marrow depression (life-threatening).
Immune system disorders:
Rare: Allergic reaction, allergic oedema/ angioedema.
Ver Rare: Anaphylactic reaction, anaphylactic shock (life threatening), 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.
Not Known: Hypoglycaemic coma.
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), hallucinations.
Very Rare: Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide).
Not Known: Mania, incl. hypomania
Nervous system disorders*:
Uncommon: Headache, dizziness, sleep disorders, taste disorders.
Rare: Par- and Dysaesthesia, hypoaesthesia, tremor, seizures (including status epilepticus), vertigo.
Very Rare: Migraine, disturbed coordination, gait disturbance, olfactory nerve disorders, intracranial hypertension and pseudotumor cerebri.
Not Known: Peripheral neuropathy and poly neuropathy.
Eye disorders*:
Rare: Visual disturbances (e.g. diplopia).
Very Rare: Visual color distortions.
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.
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, gastro-intestinal and abdominal pains, dyspepsia, flatulence.
Rare: Antibiotic associated colitis (very rarely with possible fatal outcome).
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).
Skin and subcutaneous tissues disorders:
Uncommon: Rash, pruritus, urticaria.
Rare: Photosensitivity reactions.
Very Rare: Petechiae, erythema multiforme, erythema nodosum, stevens Johnson syndrome (potentially life-threatening), toxic epidermal necrolysis (potentially life-threatening).
Not Known: Acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), fixed drug eruption.
Musculoskeletal and connective tissue disorders*:
Uncommon: Musculo skeletal pain (e.g. extremity pain, back pain, chest pain), arthralgia.
Rare: Myalgia, arthritis Increased muscle tone and cramping, tendinopathies (tendinitis, tendon rupture).
Very Rare: Muscular weakness, exacerbation of symptoms of myasthenia gravis.
Renal and urinary disorders:
Uncommon: Renal impairment
Rare: Renal failure, haematuria, crystalluria, tubulo-interstitial nephritis.
General disorders and administration site conditions*:
Uncommon: Asthenia, fever.
Rare: Oedema, sweating (hyperhidrosis).
Investigations:
Uncommon: Increase in blood alkaline phosphatase.
Rare: Increased amylase.
Not Known: International normalized 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 and neuralgia, fatigue, psychiatric symptoms (including sleep disorders, anxiety, panic attacks, depression and suicidal ideation), memory and concentration impairment, 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. A range of psychiatric symptoms may occur as part of these side effects, which may include, but are not necessarily limited to, sleep disorders, anxiety, panic attacks, confusion, or depression. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. The frequency of these prolonged, disabling and potentially irreversible serious drug reactions cannot be estimated with precision using available data, but the reporting incidence from adverse drug reaction reports indicates the frequency is at minimum between 1/1,000 and 1/10,000 (corresponding to the rare frequency category).

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

4.9. OVERDOSE:

An overdose of 12g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16g 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.

5.2. PHARMACOKINETIC PROPERTIES:

Absorption: Following oral administration of single doses of 250mg, 500mg, and 750mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentration 1-2 hours later. Single doses of 100-750mg produced dose-dependent maximum serum concentrations (C_{max}) between 0.56 and 3.7mg/L. Serum concentrations increase proportionately with doses up to 1000mg. The absolute bioavailability is approximately 70-80%. A 500mg 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 400mg 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-ionized 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 (M1), sulphociprofloxacin (M2), oxociprofloxacin (M3) and formylciprofloxacin (M4). 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. The serum elimination half-life in subjects with normal renal function is approximately 4-7 hours. 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.

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 comparable to that of other gyrase inhibitors.

Articular tolerability: As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weightbearing 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:

NOVIDAT® 250mg Tablets:

Excipients:

- Microcrystalline Cellulose
- Sodium Starch Glycolate
- Maize Starch
- Silicon Dioxide Fumed
- Magnesium Stearate
- Purified Water

Materials for coating:

- Hydroxypropyl Methyl Cellulose
- Titanium Dioxide

- Talcum Powder
- Poly Ethylene Glycol
- Simethicone LVA
- Purified Water

NOVIDAT® 500mg Tablets:

Excipients:

- Microcrystalline Cellulose
- Sodium Starch Glycolate
- Maize Starch
- Silicon Dioxide Fumed
- Magnesium Stearate
- Purified Water

Materials for coating:

- Hydroxypropyl Methyl Cellulose
- Titanium Dioxide
- Talcum Powder
- Poly Ethylene Glycol
- Simethicone LVA
- Purified Water

6.2. INCOMPATIBILITIES:

Not applicable

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Avoid exposure to heat, light and humidity. Store between 15 to 30°C
Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

NOVIDAT® 250mg Tablets: Alu/Alu blister, pack size is 10's.
NOVIDAT® 500mg Tablets: Alu/Alu blister, pack size is 10's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:

NOVIDAT® 250mg Tablets: USP Specs.
NOVIDAT® 500mg Tablets: USP Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

NOVIDAT® 250mg Tablets: 011836
NOVIDAT® 500mg Tablets: 011837

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

NOVIDAT® 250mg Tablets: 21st November, 1990
NOVIDAT® 500mg Tablets: 21st November, 1990

10. DATE OF REVISION OF THE TEXT

نوویڈیٹ ٹیبلٹ

(سپروفلاکساسن ہائیڈروکلورائیڈ)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ

کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔

NOVIDAT®
(Ciprofloxacin)

1. NAME OF THE PRODUCT
NOVIDAT® (Ciprofloxacin) Oral Suspension 125mg/5ml
NOVIDAT® (Ciprofloxacin) Oral Suspension 250mg/5ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
NOVIDAT® Oral Suspension 125mg/5ml
Each 5ml of reconstituted suspension contains:
Ciprofloxacin USP……..……125mg

NOVIDAT® Oral Suspension 250mg/5ml
Each 5ml of reconstituted suspension contains:
Ciprofloxacin USP……..……250mg

3. PHARMACEUTICAL FORM
Suspension

Appearance:
NOVIDAT® Oral Suspension 125mg/5ml: White to off-white color granules.
After reconstitution: White to off-white color suspension.
NOVIDAT® Oral Suspension 250mg/5ml: White to off-white color granules.
After reconstitution: White to off-white color suspension.

4. CLINICAL PARTICULARS
4.1. THERAPEUTIC INDICATIONS:
Because of the risk of prolonged, disabling and potentially irreversible serious adverse drug reactions this product must only be prescribed when other antibiotics that are commonly recommended for the infection are inappropriate. This applies to all indications listed below. Situations where other antibiotics are considered to be inappropriate are where:

- There is resistance to other first-line antibiotics recommended for the infection
- Other first-line antibiotics are contraindicated in an individual patient
- Other first-line antibiotics have caused side effects requiring treatment to be stopped
- Treatment with other first-line antibiotics has failed

The NOVIDAT® 250mg/5mL oral suspension is indicated for the treatment of the following infections. 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.

- Exacerbation of chronic obstructive pulmonary disease.
- 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.
- Urinary tract infections
- Uncomplicated acute cystitis.
- Acute pyelonephritis.
- Complicated urinary tract infections.
- Bacterial prostatitis
- Genital tract 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*
- Infections of the gastro-intestinal tract (e.g. traveller's diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria
- Malignant external otitis
- Infections of the bones and joints
- 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 due to *Pseudomonas aeruginosa* in patients with cystic fibrosis
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when 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.

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. 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**	**Daily dose in ml (Number of 5mL measuring spoonfuls)**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Infections of the lower respiratory tract	500mg twice daily to 750mg twice daily	10mL twice daily to 15mL twice daily (two 5mL measuring spoonfuls twice daily up to three 5mL measuring spoonfuls twice daily)	7 to 14 days

Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	500mg twice daily to 750mg twice daily	10mL twice daily to 15mL twice daily (two 5mL measuring spoonfuls twice daily up to three 5mL measuring spoonfuls twice daily)	7 to 14 days
	Chronic suppurative otitis media	500mg twice daily to 750mg twice daily	10mL twice daily to 15mL twice daily (two 5mL measuring spoonfuls twice daily up to three 5mL measuring spoonfuls twice daily)	7 to 14 days
	Malignant external otitis	750mg twice daily	15mL twice daily (three 5mL measuring spoonfuls twice daily)	28 days up to 3 months
Urinary tract infections	Uncomplicated acute cystitis	250mg twice daily to 500mg twice daily	5mL twice daily to 10mL twice daily (one 5mL measuring spoonful twice daily up to two 5mL measuring spoonfuls twice daily)	3 days
		In pre-menopausal women, 500mg single dose may be used corresponding to 10mL		

		single dose = two 5mL measuring spoonfuls as a single dose.		
	Complicated cystitis, Acute pyelonephritis	500mg twice daily	10mL twice daily (two 5mL measuring spoonfuls twice daily)	7 days
	Complicated pyelonephritis	500mg twice daily to 750mg twice daily	10mL twice daily to 15mL twice daily (two 5mL measuring spoonfuls twice daily up to three 5mL measuring spoonfuls twice daily)	At least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Bacterial Prostatitis	500mg twice daily to 750mg twice daily	10mL twice daily to 15mL twice daily. (two 5mL measuring spoonfuls twice daily up to three 5mL measuring spoonfuls twice daily)	2 to 4 weeks (acute) to 4 to 6 weeks (chronic)
Genital tract infections	Gonococcal uretritis and cervicitis due to susceptible *Neisseria gonorrhoeae*	500mg as a single dose	10mL as a single dose corresponding to two 5mL measuring spoonfuls as a single dose	1 day (single dose)
	Epididymo-orchitis and pelvic inflammatory diseases	500mg twice daily to 750mg twice daily	10mL twice daily to 15mL twice daily. (two 5mL measuring	at least 14 days

	including cases due to susceptible *Neisseria gonorrhoeae*		spoonfuls twice daily up to three 5mL measuring spoonfuls twice daily)	
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 traveller's diarrhoea	500mg twice daily	10mL twice daily (two 5mL measuring spoonfuls twice daily)	1 day
	Diarrhoea caused by *Shigella dysenteriae* type 1	500mg twice daily	10mL twice daily (two 5mL measuring spoonfuls twice daily)	5 days
	Diarrhoea caused by *Vibrio cholerae*	500mg twice daily	10mL twice daily. (two 5mL measuring spoonfuls twice daily)	3 days
	Typhoid fever	500mg twice daily	10mL twice daily. (two 5mL measuring spoonfuls twice daily)	7 days
	Intra-abdominal infections due to Gram-	500mg twice daily to 750mg twice daily	10mL twice daily to 15mL twice daily	5 to 14 days

	negative bacteria		(two 5mL measuring spoonfuls twice daily up to three 5mL measuring spoonfuls twice daily)	
Infections of the skin and soft tissue caused by Gram-negative bacteria		500mg twice daily to 750mg twice daily	10mL twice daily to 15mL twice daily (two 5mL measuring spoonfuls twice daily up to three 5mL measuring spoonfuls twice daily)	7 to 14 days
Bone and joint infections		500mg twice daily to 750mg twice daily	10mL twice daily to 15mL twice daily. (two 5mL measuring spoonfuls twice daily up to three 5mL measuring spoonfuls twice daily)	Max. of 3 months
Neutropenic patients with fever that is suspected to be due to a bacterial infection. Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance		500mg twice daily to 750mg twice daily	10mL twice daily to 15mL twice daily. (two 5mL measuring spoonfuls twice daily up to three 5mL measuring spoonfuls twice daily)	Therapy should be continued over the entire period of neutropenia

Prophylaxis of invasive infections due to *Neisseria meningitidis*	500mg as a single dose	10mL as a single dose corresponding to two 5mL measuring spoonfuls 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.	500mg twice daily	10mL twice daily (two 5mL measuring spoonfuls twice daily)	60 days from the confirmation of *Bacillus anthracis* exposure

Paediatric population:

Indications	**Daily dose in mg and in mL** For practical guidance on the number of measuring spoonfuls, refer to table A below	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Cystic fibrosis	20mg/kg body weight twice daily with a maximum of 750mg per dose, corresponding to a 0.4mL/kg body weight twice daily with a maximum of 15mL per each of the two daily administrations for the 250mg/5mL suspension	10 to 14 days
Complicated urinary tract infections and pyelonephritis	10mg/kg body weight twice daily to 20mg/kg body weight twice daily with a maximum of 750mg per dose, corresponding to a	10 to 21 days

	0.2mL/kg body weight twice daily to 0.4mL/kg body weight twice daily with a maximum of 15mL per each of the two daily administrations for the 250mg/5mL suspension	
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.	10mg/kg body weight twice daily to 15mg/kg body weight twice daily with a maximum of 500mg per dose, corresponding to a 0.2mL/kg body weight twice daily to 0.3mL/kg body weight twice daily with a maximum of 10mL per each of the two daily administrations for the 250mg/5mL suspension.	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	20mg/kg body weight twice daily with a maximum of 750mg per dose, corresponding to a 0.4mL/kg body weight twice daily with a maximum of 15mL per each of the two daily administrations for the 250mg/5mL suspension.	According to the type of infections

Table A: 250mg/5mL oral suspension – Practical guidance on the number of measuring spoonfuls to be administered twice daily (every 12 hours)

250mg/5mL oral suspension
½ spoon = 125mg; 1 spoon = 250mg; 1 spoon + ½ spoon = 375mg; 2 spoons = 500mg; 2 spoons + ½ spoon = 625mg; 3 spoons = 750mg (max dose)

Body weight (kg)	Practical guidance for each of the two daily administrations of NOVIDAT® oral suspension per recommended dose in mg/kg bodyweight and indications as stated above	
	10mg/kg	**20mg/kg**
9-10kg	½ spoon	1 spoon*
11-15kg	½ spoon	1 spoon
16-20mg	1 spoon	1 spoon + ½ spoon
21-25kg	1 spoon	2 spoons
26-28kg	1 spoon	2 spoons + ½ spoon
29-31kg	1 spoon + ½ spoon	2 spoons + ½ spoon
32-40kg	1 spoon + ½ spoon	3 spoons
41-51kg	2 spoons	3 spoons
52-61kg	2 spoons + ½ spoon	3 spoons
62kg and above	3 spoons	3 spoons
* The administration of number of measuring spoonfuls leads to an actual dose more than 20% above the recommended maximum dose per bodyweight		

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

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:
Oral suspension can be taken independent of mealtimes.
If a dose is missed, it should be taken anytime but not later than 6 hours prior to the next scheduled dose. If less than 6 hours remain before the next dose,

the missed dose should not be taken and treatment should be continued as prescribed with the next scheduled dose. Double doses should not be taken to compensate for a missed dose. If taken on an empty stomach, the active substance is absorbed more rapidly.

Ciprofloxacin oral suspension can be taken during meals containing dairy products or mineral-fortified drinks. However, ciprofloxacin oral suspension should not be administered concurrently with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit juice (e.g. calcium-fortified orange juice) when these products or drinks are taken alone outside meals. Nevertheless, ciprofloxacin oral suspension could be administered either 1-2 hours before or at least 4 hours after dairy products or mineral-fortified drinks when these products and drinks are taken alone outside meals, such as recommended for drugs containing calcium.

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

DIRECTION FOR RECONSTITUTION:

Shake bottle to loosen the mass. Add completely filled freshly boiled and cooled water by the provided cup (17ml) into bottle and shake vigorously.

Repeat the procedure with an additional 17ml of freshly boiled and cooled water and shake vigorously to form uniform suspension.

4.3. CONTRAINDICATIONS:

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients.
- Concomitant administration of ciprofloxacin and tizanidine

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. Treatment of these patients with Ciprofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.

Prolonged, disabling and potentially irreversible serious adverse drug reactions: Cases of prolonged (continuing for months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (including musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. Ciprofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be

advised to contact their prescriber for advice, so that symptoms can be appropriately investigated and to avoid further exposure which could potentially worsen adverse reactions.

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: Gonococcal urethritis, cervicitis, epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae* isolates. Therefore, Ciprofloxacin 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: 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. The single dose of ciprofloxacin that may be used in uncomplicated cystitis in pre-menopausal women is expected to be associated with lower efficacy than with 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.

Traveller's 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. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue.

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 the results of the microbiological documentation.

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 and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

Tendinitis and tendon rupture: Ciprofloxacin 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, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the events of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin. 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, 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.

Patients with myasthenia gravis: Ciprofloxacin should be used with caution in patients with myasthenia gravis, because symptoms can be exacerbated.

Aortic aneurysm and dissection, and heart valve regurgitation/ incompetence: Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/ incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones. 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 congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection or heart valves disease, or in presence of other risk factors or conditions predisposing.

- For both aortic aneurysm and dissection and heart valve regurgitation/ incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis or additionally.
- For aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or additionally.
- For heart valve regurgitation/incompetence (e.g. infective endocarditis).

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

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

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.

Seizures: Ciprofloxacin like other quinolones is 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.

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.

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

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-arrhythmic, 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.

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

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. 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. 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 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. 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 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, agomelatine). Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary. Co-administration of ciprofloxacin and tizanidine is contraindicated.

Methotrexate: The concomitant use of ciprofloxacin with methotrexate is not recommended.

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.

Information about excipients:

Sucrose Load: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or saccharose-isomaltase deficiency, should not take **NOVIDAT®** 250mg/5mL. As **NOVIDAT®** 250mg/5mL suspension contains 1.4g sucrose per 5mL measuring spoonful, this has to be taken into consideration in terms of daily intake. This is to be considered in patients with diabetes mellitus. **NOVIDAT®** 250mg/5mL can be harmful to teeth.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS:

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).

Chelation Complex Formation: The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer or lanthanum carbonate), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin. Consequently,

ciprofloxacin 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 H2 receptor blockers.

Food and Dairy Products: Dietary calcium as part of a meal does not significantly affect absorption of ciprofloxacin (oral). However, ciprofloxacin oral suspension administered concurrently with dairy products or mineral-fortified drinks (e.g. milk, yoghurt, calcium-fortified orange juice) when these products or drinks are taken alone outside meals, may reduce the absorption of ciprofloxacin. Consequently, ciprofloxacin oral suspension can be taken during meals containing dairy products or mineral-fortified drinks. The concurrent administration of dairy products or mineral-fortified drinks taken alone outside meals, with ciprofloxacin oral suspension should be avoided. However, ciprofloxacin oral suspension could be administered either 1-2 hours before or at least 4 hours after dairy products or mineral-fortified drinks when these products and drinks are taken alone outside meals, such as recommended for drugs containing calcium.

See also above paragraph Chelation Complex Formation.

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

Metoclopramide: Metoclopramide accelerates the absorption of ciprofloxacin (oral) resulting in a shorter time to reach maximum plasma concentrations. No effect was seen 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: Tizanidine must not be administered together with ciprofloxacin. There is 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.

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.

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.
Ciclosporin: A transient rise in the concentration of serum creatinine was observed when ciprofloxacin and ciclosporin containing medicinal products were administered simultaneously. Therefore, it is frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.
Vitamin K antagonists: Simultaneous administration of ciprofloxacin with a vitamin K antagonist may augment its anti-coagulant effects. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalized ratio) is difficult to assess. The INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with a vitamin K antagonist (e.g. warfarin, acenocoumarol, phenprocoumon or fluindione).
Duloxetine: 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.
Ropinirole: 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 coadministration with ciprofloxacin.
Lidocaine: 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 is well tolerated, a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.
Clozapine: Following concomitant administration of 250mg 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.
Sildenafil: Caution should be used prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.
Agomelatine: 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

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. It is not recommended to use ciprofloxacin oral suspension during pregnancy.

Breast-feeding: Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, based on animal data, and because this medicine also contains benzyl alcohol, which may accumulate and a risk in the breastfed child cannot be excluded, ciprofloxacin oral suspension is not recommended for use 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.

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 grouping is defined using the following convention:

Very common (≥ 1/10); Common (≥ 1/100 to <1/10); Uncommon (≥ 1/1000 to 1/100); Rare (≥ 1/10,000 to < 1/1000); Very Rare (<1/10,000) and Not known (cannot be estimated from the available data).

The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

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/ angio-oedema

Very Rare: Anaphylactic reaction, anaphylactic shock (life-threatening), 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

Not Known: Hypoglycaemic coma

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), hallucinations

Very Rare: Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide).

Not Known: Mania, including hypomania

Nervous system disorders*:

Uncommon: Headache, dizziness, sleep disorders, taste disorders

Rare: Par- and Dysaesthesia, hypoaesthesia, tremor, seizures (including status epilepticus), vertigo

Very Rare: Migraine, disturbed co-ordination, gait disturbance, olfactory nerve disorders, intracranial hypertension and pseudotumor cerebri

Not Known: Peripheral neuropathy and polyneuropathy

Eye disorders*:

Rare: Visual disturbances (e.g. diplopia)

Very Rare: Visual color distortions

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

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, gastro-intestinal and abdominal pains, dyspepsia, flatulence

Rare: Antibiotic associated colitis (very rarely with possible fatal outcome)
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)
Skin and subcutaneous tissues disorders:
Uncommon: Rash, pruritus, urticaria
Rare: Photosensitivity reactions
Very Rare: Petechiae, erythema multiforme, erythema nodosum, stevens-Johnson syndrome (potentially life-threatening), toxic epidermal necrolysis (potentially life-threatening)
Not Known: Acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders*:
Uncommon: Musculoskeletal pain (e.g. extremity pain, back pain, chest pain), arthralgia
Rare: Myalgia, arthritis, increased muscle tone and cramping, tendinopathies (tendinitis, tendon rupture predominantly Achilles tendon)
Very Rare: Muscular weakness, exacerbation of symptoms of myasthenia gravis
Renal and urinary disorders:
Uncommon: Renal impairment
Rare: Renal failure, haematuria, crystalluria, tubulo-interstitial nephritis
General disorders and administration site conditions*:
Uncommon: Asthenia, fever
Rare: Oedema, sweating (hyperhidrosis)
Investigations:
Uncommon: Increase in blood alkaline phosphatase
Rare: Increased amylase
Not Known: International normalized ratio increased (in patients treated with Vitamin K antagonists)
* 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, fatigue, psychiatric symptoms (including sleep disorders, anxiety, panic attacks, depression and suicidal ideation), memory and concentration impairment, 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. A range of psychiatric symptoms may occur as part of these side effects, which may include, but are not necessarily limited to, sleep disorders, anxiety, panic

attacks, confusion, or depression. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. The frequency of these prolonged, disabling and potentially irreversible serious drug reactions cannot be estimated with precision using available data, but the reporting incidence from adverse drug reaction reports indicates the frequency is at minimum between 1/1,000 and 1/10,000 (corresponding to the rare frequency category). ** Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones.

4.9. OVERDOSE:

An overdose of 12g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16g 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.

5.2. PHARMACOKINETIC PROPERTIES:

Absorption: Following oral administration of single doses of 250mg, 500mg, and 750mg 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 100-750mg produced dose-dependent maximum serum concentrations (C_{max}) between 0.56 and 3.7mg/L. Serum concentrations increase proportionately with doses up to 1000mg. The absolute bioavailability is approximately 70-80%. A 500mg 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 400mg ciprofloxacin given over 60 minutes every 12 hours. The pharmacokinetics of ciprofloxacin oral suspension 250mg/5mL and 500mg/5mL are similar to those of tablets.

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 2-3L/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 (M1), sulphociprofloxacin (M2), oxociprofloxacin (M3) and formylciprofloxacin (M4). 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 CYP450 1A2 iso-enzymes.

Elimination: Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally. The serum elimination half-life in subjects with normal renal function is approximately 4-7 hours. Renal clearance is between 180-300mL/kg/h and the total body clearance is between 480- 600ml/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion.

Severely impaired renal function leads to increased half-lives of ciprofloxacin of up to 12h. 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.

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 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:

NOVIDAT® Oral Suspension 125mg/5ml:

- Xanthan Gum
- MCC & CMC NA
- Neotame Powder
- Sucrose
- Aspartame Powder
- Pineapple Powder Flavour
- Sodium Citrate
- Silicon Dioxide Fumed
- Magnesium Stearate
- Sorbitol Powder
- Titanium Dioxide
- Peppermint Flavor

NOVIDAT® Oral Suspension 250mg/5ml:

- Xanthan Gum
- MCC & CMC NA
- Neotame Powder
- Sucrose

- Aspartame Powder
- Pineapple Powder Flavour
- Sodium Citrate
- Silicon Dioxide Fumed
- Magnesium Stearate
- Sorbitol Powder
- Titanium Dioxide
- Peppermint Flavor

6.2. INCOMPATIBILITIES:

No additions should be made to the mixed final ciprofloxacin suspension.

6.3. SHELF LIFE:

Unopened bottle: See expiry on the pack.
Reconstituted suspension: 14 days.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Do not store over 30°C, and protect from heat, light and moisture.
Improper storage may deteriorate the medicine.
Keep out of reach of children.
The reconstituted suspension should be kept at room temperature (below 25°C), so that potency of the product remains stable and be used within 14 days.

6.5. NATURE AND CONTENTS OF CONTAINER:

NOVIDAT® Oral Suspension 125mg/5ml: Amber glass bottle with tamper-proof aluminium cap with conical plug. 17ml measuring cup and a measuring spoon also present. Bottle size is 90ml & pack size is 60ml.
NOVIDAT® Oral Suspension 250mg/5ml: Amber glass bottle with tamper-proof aluminium cap with conical plug. 17ml measuring cup and a measuring spoon also present. Bottle size is 90ml & pack size is 60ml.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:

NOVIDAT® Oral Suspension 125mg/5ml: USP Specs.
NOVIDAT® Oral Suspension 250mg/5ml: USP Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

NOVIDAT® Oral Suspension 125mg/5ml: 067166
NOVIDAT® Oral Suspension 250mg/5ml: 047142

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

NOVIDAT® Oral Suspension 125mg/5ml: 2nd December, 2010
NOVIDAT® Oral Suspension 250mg/5ml: 21st September, 2007

10. DATE OF REVISION OF THE TEXT

نوویڈیٹ اورل سسپینشن

(سپروفلاکساسن)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،
گرمی، روشنی اور نمی سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی۔
تیار شدہ سسپینشن کو کمرے کے درجہ حرارت (۲۵ ڈگری سینٹی گریڈ سے کم) پر رکھیں
تاکہ دوا کی تاثیر برقرار رہے اور ۱۴ یوم کے اندر استعمال کرلیں۔

NOVIDAT® / NOVIDAT® DS
(Ciprofloxacin) (Ciprofloxacin)

1. NAME OF THE PRODUCT
NOVIDAT® (Ciprofloxacin) Injection 200mg/100ml
NOVIDAT® DS (Ciprofloxacin) Injection 400mg/100ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
NOVIDAT® Injection 200mg/100ml
Each 100ml contains:
Ciprofloxacin USP.....200mg

NOVIDAT® DS Injection 400mg/100ml
Each 100ml contains:
Ciprofloxacin USP…….....400mg

3. PHARMACEUTICAL FORM
Solution for Injection

Appearance:
NOVIDAT® Injection 200mg/100ml: Clear colorless to slightly colored solution free from any visible particles.
NOVIDAT® DS Injection 400mg/100ml: Clear colorless to slightly colored solution free from any visible particles.

4. CLINICAL PARTICULARS
4.1. THERAPEUTIC INDICATIONS:
NOVIDAT® is indicated for the treatment of the following infections. 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
  - Exacerbation of chronic obstructive pulmonary disease.
  - Broncho-pulmonary infections in cystic fibrosis or in bronchiectasis.
  - Pneumonia

In exacerbation of chronic obstructive pulmonary disease, NOVIDAT® should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.
- 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. traveler's diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria
- Malignant external otitis
- Infections of the bones and joints
- 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 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. 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 in mg**	**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	Acute exacerbation of chronic sinusitis	400mg twice daily to 400mg three times a day	7 to 14 days
	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	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	400mg twice daily	1 day

	Shigella dysenteriae type 1 and empirical treatment of severe travelers' diarrhoea		
	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
Infections of the skin and soft tissue		400mg twice daily to 400mg three times a day	7 to 14 days
Bone and joint infections		400mg twice daily to 400mg three times a day	max. of 3 months
Neutropenic patients with fever that is suspected to be due to a bacterial infection. 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 in mg**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
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: Elderly patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.
Renal and hepatic impairment: Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min/1.73 m²]	**Serum Creatinine [µmol/L]**	**Intravenous Dose [mg]**
>60	<124	See Usual Dosage.
30-60	124 to 168	200-400mg every 12h
<30	>169	200-400mg every 24h

Patients on haemodialysis	>169	200-400mg every 24h (after dialysis)
Patients on peritoneal dialysis	>169	200-400mg every 24h

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:
NOVIDAT® should be checked visually prior to use. It must not be used if cloudy.
NOVIDAT® should be administered by intravenous infusion. For children, the infusion duration is 60 minutes.
In adult patients, infusion time is 60 minutes for 400mg **NOVIDAT® DS** and 30 minutes for 200mg **NOVIDAT®** Injection. 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.

4.3. CONTRAINDICATIONS:

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients.
- Concomitant administration of ciprofloxacin and tizanidine.

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. Treatment of these patients with ciprofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.
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* isolates. For epididymo-orchitis and pelvic inflammatory diseases, empirical ciprofloxacin should only be considered in combination with another appropriate

antibacterial agent (e.g. a cephalosporin) unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. 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. 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.

Travelers' 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.

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 the results of the microbiological documentation.

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.

Aortic aneurysm and dissection, and heart valve regurgitation/ incompetence: 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 congenital heart

valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection or heart valve disease, or in presence of other risk factors or conditions predisposing:

- For both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome, or Ehlers-Danlos syndrome, Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis) or additionally.
- For aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or additionally.
- For heart valve regurgitation/incompetence (e.g. infective endocarditis).

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

Hypersensitivity: Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose and may be life threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

Prolonged, disabling and potentially irreversible serious adverse drug reactions: Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. Ciprofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

Musculoskeletal System: Ciprofloxacin 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, ciprofloxacin 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: 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. immobilization). Corticosteroids should not be used if signs of tendinopathy occur.

Myasthenia gravis: Ciprofloxacin should be used with caution in patients with myasthenia gravis, because symptoms can be exacerbated.

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

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.

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. Psychiatric reactions may occur even after first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to suicidal ideations/thoughts culminating in attempted suicide or completed suicide. In the occurrence of such cases, ciprofloxacin should be discontinued. Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin.

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.

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.

Dysglycaemia: As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported, 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.

Gastro-intestinal 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. 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. 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 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. 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 metabolized by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine, duloxetine, agomelatine). Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for

clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary. Co-administration of ciprofloxacin and tizanidine is contra-indicated.

Methotrexate: The concomitant use of ciprofloxacin with methotrexate is not recommended.

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.

Sodium: This medicinal product contains 354.1mg of sodium per vial, equivalent to 17.7% of the WHO recommended maximum daily intake of 2g of sodium for an adult. The maximum daily dose of this medicinal product is equivalent to 106.2% of the recommended maximum daily intake of sodium for an adult.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

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).

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. 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

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

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.

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

Vitamin K antagonists: Simultaneous administration of ciprofloxacin with a vitamin K antagonist may augment its anti-coagulant effects. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalized ratio) is difficult to assess. The INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with a vitamin K antagonist (e.g., warfarin, acenocoumarol, phenprocoumon, or fluindione).

Duloxetine: 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.

Ropinirole: 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.

Lidocaine: Lidocaine treatment is well tolerated, a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.

Clozapine: Following concomitant administration of 250mg 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.

Sildenafil: Caution should be used prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.

Agomelatine: 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.

Zolpidem: Co-administration of 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 foeto/neonatal toxicity of ciprofloxacin. 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. 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, 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, 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 grouping is defined using the following convention: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥1/1000 to < 1/100); Rare (≥ 1/10,000 to < 1/1000); Very Rare (< 1/10,000); and Not known (cannot be estimated from the available data). The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

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), 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.
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), hallucinations.
Very Rare: Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide).
Not Known: Mania, including hypomania
Nervous system disorders*:
Uncommon: Headache, dizziness, sleep disorders, taste disorders
Rare: Par- and Dysaesthesia, hypoaesthesia, tremor, seizures (incl. status epilepticus), vertigo
Very Rare: Migraine, disturbed co-ordination, gait disturbance, olfactory nerve disorders, intracranial hypertension and pseudotumor cerebri
Not Known: Peripheral neuropathy and polyneuropathy
Eye disorders*:
Rare: Visual disturbances (e.g. diplopia)
Very Rare: Visual color distortions
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
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, gastro-intestinal and abdominal pains, dyspepsia, flatulence
Rare: Antibiotic associated colitis (very rarely with possible fatal outcome)
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)

Skin and subcutaneous tissues disorders:

Uncommon: Rash, pruritus, urticaria

Rare: Photosensitivity reactions

Very Rare: Petechiae erythema multiforme erythema nodosum Stevens-Johnson syndrome (potentially life-threatening), toxic epidermal necrolysis (potentially life-threatening)

Not Known: Acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS)

Musculoskeletal and connective tissue disorders*:

Uncommon: Musculo skeletal pain (e.g. extremity pain, back pain, chest pain), Arthralgia

Rare: Myalgia Arthritis Increased muscle tone and cramping Tendinopathies (tendinitis, tendon rupture)

Very Rare: Muscular weakness, exacerbation of symptoms of myasthenia gravis

Renal and urinary disorders:

Uncommon: Renal impairment

Rare: Renal failure, haematuria, crystalluria, tubulo-interstitial nephritis

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: Increased amylase

Not Known: International normalized 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 tendinitis, 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.

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

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, vsual 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 (arthralgie, arthrite), mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly.

4.9. OVERDOSE:

An overdose of 12g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16g 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. 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 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: 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. 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.

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 400mg 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 200mg ciprofloxacin or the oral administration of 250mg ciprofloxacin, both given every 12 hours, produced an equivalent area under the serum concentration time curve (AUC). A 60-minute intravenous infusion of 400mg ciprofloxacin every 12 hours was bioequivalent to a 500mg oral dose every 12 hours with regard to AUC. The 400mg intravenous dose administered over 60 minutes every 12 hours resulted in a C_{max} similar to that observed with a 750mg oral dose. A 60-minute infusion of 400mg ciprofloxacin every 8 hours is equivalent with respect to AUC to 750mg oral regimen given every 12 hours.

Distribution: Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionized 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 (M1), sulphociprofloxacin (M2), oxociprofloxacin (M3) and formylciprofloxacin (M4).

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, feacally. Renal clearance is between 180-300mL/kg/h and the total body clearance is between 480-600mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half-lives of ciprofloxacin of up to 12h. 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 concentration.

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 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:

NOVIDAT® Injection 200mg/100ml:

- Sodium Chloride
- Lactic Acid 90%
- Disodium EDTA
- Activated Charcoal
- Water for Injection

NOVIDAT® DS Injection 400mg/100ml:

- Sodium Chloride
- Lactic Acid 90%
- Disodium EDTA
- Activated Charcoal
- Water for Injection

6.2. INCOMPATIBILITIES:

This medicinal product must not be mixed with other medicinal products except following:

- 0.9% Sodium Chloride Solution
- Ringer' Solution
- Ringer's Lactate Solution
- 10% Glucose Solution
- 5% Fructose Solution.

Compatibility with these solutions has been proven in ciprofloxacin concentrations of 1mg/ml. 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).

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Do not store over 30°C, and protect from heat, light and freezing.
Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

NOVIDAT® Injection 200mg/100ml: Clear 100ml glass bottle (USP type-II) with bromobutyl stopper, sealed with tear-off seal, pack size is 1's.
NOVIDAT® DS Injection 400mg/100ml: Clear 100ml glass bottle (USP type-II) with bromobutyl stopper, sealed with tear-off seal, pack size is 1's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

For single use only. Since the infusion solution is photosensitive, the infusion bags should be removed from the opaque overwrap only immediately before use. To be used immediately after the bag is opened. The diluted solution should be inspected visually for particulate matter and discoloration prior administration. Use only clear, colourless to slightly yellow solution and undamaged containers. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:

NOVIDAT® Injection 200mg/100ml: USP Specs.
NOVIDAT® DS Injection 400mg/100ml: USP Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufacturing & Release Site:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

Packing Site:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-140/A, S.I.T.E., Karachi-Pakistan
Mfg Lic. No. 000938

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

NOVIDAT® Injection 200mg/100ml: 012066
NOVIDAT® DS Injection 400mg/100ml: 042270

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

NOVIDAT® Injection 200mg/100ml: 26th December, 1990
NOVIDAT® DS Injection 400mg/100ml: 21st March, 2006

10. DATE OF REVISION OF THE TEXT

نوویڈیٹ انجکشن (سپروفلاکسا سن) / **نوویڈیٹ** ڈی ایس انجکشن (سپروفلاکسا سن)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،

گرمی، روشنی اور منجمد ہونے سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی۔

انجکشن کے لیک ہونے، دُھندلا ہونے یا اس میں کوئی غیر حل

پزیر شے نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔