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NOVIDAT®
(Ciprofloxacin HCl)

Tablets / Dry Powder For Suspension

WARNING: Serious Adverse Reactions Including Tendinitis, Tendon Rupture, Peripheral Neuropathy, Central Nervous System Effects & Exacerbation Of Myasthenia Gravis

Fluoroquinolones, including ciprofloxacin, have been are associated with disabling and potentially irreversible serious adverse reactions that have occurred together including: ● Tendinitis and tendon rupture ● Peripheral neuropathy ● Central nervous system effects
Discontinue ciprofloxacin immediately and avoid the use of fluoroquinolone, including ciprofloxacin, in patients who experience any of these serious adverse reactions. Fluoroquinolones, including ciprofloxacin, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid ciprofloxacin in patients with known history of myasthenia gravis. Because fluoroquinolone, including ciprofloxacin, have been associated with serious adverse reactions, reserve ciprofloxacin for use in patients who have no alternative treatment options for the following indications: ● Acute exacerbation of chronic bronchitis ● Acute uncomplicated cystitis ● Acute sinusitis

QUALITATIVE AND QUANTITATIVE COMPOSITION

NOVIDAT® 250mg Tablets
Each film coated tablet contains:
Ciprofloxacin HCl USP eq. to Ciprofloxacin....250mg

NOVIDAT® 500mg Tablets
Each film coated tablet contains:
Ciprofloxacin HCl USP eq. to Ciprofloxacin....500mg

NOVIDAT® Dry Powder for Suspension 125mg
Each 5ml of reconstituted suspension contains:
Ciprofloxacin HCl USP eq. to Ciprofloxacin.....125mg

NOVIDAT® Dry Powder for Suspension 250mg
Each 5ml of reconstituted suspension contains:
Ciprofloxacin HCl USP eq. to Ciprofloxacin.....250mg

PHARMACEUTICAL FORM: Tablets / Suspension

CLINICAL PARTICULARS: THERAPEUTIC INDICATIONS: NOVIDAT® tablets & suspension are 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 ○ Pneumonia ○ Broncho-pulmonary infections in cystic fibrosis or in bronchiectasis ● Chronic suppurative otitis media ● Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria ● Acute pyelonephritis ● Complicated urinary tract infections ● Bacterial prostatitis ● Genital tract infections ○ Gonococcal urethritis 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* ● Intra-abdominal infections ● Infections of the skin and soft tissue caused by Gram-negative bacteria ● Infections of the bones and joints ● Inhalation anthrax (post-exposure prophylaxis and curative treatment) Ciprofloxacin may be used in the management of neutropenia patients with fever that is suspected to be due to a bacterial infection. ***In exacerbations of chronic obstructive pulmonary disease:*** Ciprofloxacin should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections. ***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. **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. ***Infants, Children, Adolescents, & Adults:*** ● Prophylaxis to reduce incidence or progression of disease following inhalation exposure to *Bacillus anthracis* (Inhalational Anthrax post-exposure) ● Prophylaxis and treatment of plague *(Yersinia pestis).* ● Ciprofloxacin is not a drug of first choice in the paediatric population due to associated risk of arthropathy and histopathological changes in weight-bearing joints.

POSOLOGY & METHOD OF ADMINISTRATION: Posology: The determination of dosage and duration for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative microorganism, the integrity of the patient's host-defense mechanisms, and the status of renal & hepatic function. **NOVIDAT®** Tablets or Oral Suspension may be administered to adult patients when clinically indicated at the discretion of the physician.

Adult Dosage Guidelines:

Indications		Daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Infections of the lower respiratory tract		500mg b.i.d. to 750mg b.i.d.	7 to 14 days
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	500mg b.i.d. to 750mg b.i.d.	7 to 14 days
	Chronic suppurative otitis media	500mg b.i.d. to 750mg b.i.d.	7 to 14 days
	Malignant external otitis	750mg b.i.d.	28 days up to 3 months
Urinary tract infections	Uncomplicated acute cystitis	250mg b.i.d. to 500mg b.i.d.	3 days
		In pre-menopausal women, 500mg single dose may be used	
	Complicated cystitis, Acute pyelonephritis	500mg b.i.d.	7 days
	Complicated pyelonephritis	500mg b.i.d. to 750mg b.i.d.	at least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Bacterial prostatitis	500mg b.i.d. to 750mg b.i.d.	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 & pelvic inflammatory diseases including cases due to susceptible *Neisseria gonorrhoeae*	500mg b.i.d. to 750mg b.i.d.	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 & empirical treatment of severe travellers' diarrhoea	500mg b.i.d.	1 day
	Diarrhoea caused by *Shigella dysenteriae* type 1	500mg b.i.d.	5 days
	Diarrhoea caused by *Vibrio cholerae*	500mg b.i.d.	3 days
	Typhoid fever	500mg b.i.d.	7 days
	Intra-abdominal infections due to Gram-negative bacteria	500mg b.i.d. to 750mg b.i.d.	5 to 14 days
Infections of the skin and soft tissue caused by Gram-negative bacteria		500mg b.i.d. to 750mg b.i.d.	7 to 14 days
Bone and joint infections		500mg b.i.d. to 750mg b.i.d.	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 b.i.d. to 750mg b.i.d.	Therapy should be continued over the entire period of neutropenia
Prophylaxis of invasive infections due to *Neisseria meningitidis*		500mg as a single dose	1 day (single dose)
Inhalation anthrax post-exposure prophylaxis & 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 b.i.d.	60 days from the confirmation of *Bacillus anthracis* exposure

1. Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared, except for inhalational anthrax (post-exposure). 2. Used in conjunction with metronidazole. 3. Begin drug administration as soon as possible after suspected or confirmed exposure.

Conversion of IV to Oral Dosing in Adults: Patients whose therapy is started with **NOVIDAT®** IV may be switched to **NOVIDAT®** Tablets or Oral Suspension when clinically indicated at the discretion of the physician

Equivalent AUC Dosing Regimens:

NOVIDAT® Oral Dosage	Equivalent NOVIDAT® IV Dosage
250mg tablet every 12 hours	200mg intravenous every 12 hours
500mg tablet every 12 hours	400mg intravenous every 12 hours

Paediatric Dosage Guidelines:

Indications	Daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Cystic fibrosis	20mg/kg body weight b.i.d. with a max. of 750mg per dose.	10 to 14 days
Complicated urinary tract infections and acute pyelonephritis	10mg/kg body weight b.i.d. to 20mg/kg body weight b.i.d. with a max. of 750mg per dose.	10 to 21 days
Inhalation anthrax post-exposure prophylaxis & 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 b.i.d. to 15mg/kg body weight b.i.d. with a max. of 500mg per dose.	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	20mg/kg body weight b.i.d. with a max. 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/1.73 m²]	Serum Creatinine [µmol/L]	Oral Dose [mg]
> 60	< 124	See Usual Dosage.
30-60	124 to 168	250-500mg every 12 h
< 30	> 169	250-500mg every 24 h
Patients on hemodialysis	> 169	250-500mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	250-500mg every 24 h

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

Method of administration: 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. 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. **Important Administration Instructions:** ***With Multivalent Cations:*** Administer **NOVIDAT®** at least 2 hours before or 6 hours after magnesium/aluminum antacids; polymeric phosphate binders (for example, sevelamer, lanthanum carbonate) or sucralfate; didanosine chewable/buffered tablets or paediatric powder for oral solution; other highly buffered drugs; or other products containing calcium, iron or zinc. **With Dairy Products:** Concomitant administration of **NOVIDAT®** with dairy products (like milk or yogurt) or calcium-fortified juices alone should be avoided since decreased absorption is possible; however, **NOVIDAT®** may be taken with a meal that contains these products. **Hydration of Patients Receiving NOVIDAT®:** Assure adequate hydration of patients receiving **NOVIDAT®** to prevent the formation of highly concentrated urine. Crystalluria has been reported with quinolones. Instruct the patient of the appropriate **NOVIDAT®** administration. **Missed Doses:** 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.

Dosing of NOVIDAT® for Oral Suspension using the Co-Packaged Spoon in Adults and Paediatric Patients (5% NOVIDAT® for Oral Suspension: 250mg ciprofloxacin per 5mL after reconstitution)

Infection	Body weight (kg)	Dose by Measuring Spoonful (s) using Co-Packed Spoon* (teaspoonful (s) (volume (mL))	Dose Strength
Complicated Urinary Tract or Pyelonephritis (patients from 1 to 17 years of age)[1] and Plague[2]	9kg to 12kg	½ teaspoonful (2.5mL)	125mg
	13kg to 18kg	1 teaspoonful (5mL)	250mg
	19 kg to 24kg	1 to 1 ½ teaspoonful(s) (5mL to 7.5mL)	250mg to 375mg
	25 kg to 31kg	1 ½ to 2 teaspoonful's (7.5mL to 10mL)	375mg to 500mg
	32kg to 37kg	1 ½ to 2 ½ teaspoonful's (7.5mL to 12.5mL)	375mg to 625mg
	38kg or more	2 to 3 teaspoonful's (10mL to 15mL)	500mg to 750mg
Inhalational Anthrax (Post Exposure)[3]	9kg to 12kg	½ teaspoonful (2.5mL)	125mg
	13kg to 18kg	1 teaspoonful (5mL)	250mg
	19kg to 24kg	1 to 1 ½ teaspoonful(s) (5mL to 7.5mL)	250mg to 375mg
	25kg or more	2 teaspoonful's (10mL)	500mg

1. Administer every 12 hours for 10-21 days. 2. Administer every 8-12 hours for 10-21 days for paediatric patients; for adults administer every 12 hours for 14 days. 3. Administer every 12 hours for 60 days.

CONTRAINDICATIONS: ● Hypersensitivity to the active substance to other quinolone or to any of the excipients. ● Concomitant administration of ciprofloxacin and tizanidine.

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 urethritis 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 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. **Travellers' diarrhoea:** The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited. **Infections of the bones and joints:** Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation. **Inhalational anthrax:** Use in humans is based on *in-vitro* susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax. **Paediatric population:** The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents. **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:** Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. Ciprofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice. **Tendinitis and tendon rupture:** 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 (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. **Patients with myasthenia gravis:** Ciprofloxacin should be used with caution in patients with myasthenia gravis, because symptoms can be exacerbated. **Aortic aneurysm and dissection:** Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis). In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department. **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 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. **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-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 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 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 metabolised by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine, duloxetine, agomelatine). Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be

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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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION: Effects of other products on ciprofloxacin: ***Drugs known to prolong QT interval:*** Ciprofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics). ***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. However, the concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yogurt, 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. 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. ***Cyclosporin:*** A transient rise in the concentration of serum creatinine was observed when ciprofloxacin and cydosporin 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:*** In clinical studies, it was demonstrated that concomitant use of duloxetine with strong inhibitors of the CYP450 1A2 isoenzyme 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:*** Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin. ***Lidocaine:*** Lidocaine treatment was 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. ***Sildenafil:*** C_{max} and AUC of sildenafil were increased approximately twofold in healthy subjects after an oral dose of 50mg given concomitantly with 500mg ciprofloxacin. Therefore, caution should be used prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits. ***Agomelatine:*** In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedly inhibits the metabolism of agomelatine resulting in a 60-fold increase of agomelatine exposure. ***Zolpidem:*** Co-administration of ciprofloxacin may increase blood levels of zolpidem, concurrent use is not recommended.

PREGNANCY AND LACTATION: Pregnancy: The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or fetal/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 / fetus. 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.

UNDESIRABLE EFFECTS: The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Very Rare < 1/10,000	Frequency not known (cannot be estimated from the available data)
Infections & Infestations		Mycotic super-infections			
Blood & Lymphatic System Disorders		Eosinophilia	Leukopenia, Anaemia, Neutropenia, Leukocytosis, Thrombocytopenia, Thrombocytaemia	Haemolytic anaemia, Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction, Allergic oedema / angiooedema	Anaphylactic reaction, Anaphylactic shock (life-threatening),Serum sickness -likereaction	
Endocrine disorders					Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Metabolism and Nutrition Disorders		Decreased appetite	Hyperglycaemia Hypoglycaemia		Hypoglycaemic coma
Psychiatric Disorders*		Psychomotor hyperactivity / agitation	Confusion & disorientation, Anxiety reaction, Abnormal dreams, Depression (potentially culminating in suicidal ideations/thoughts or suicide attempts & completed suicide) Hallucinations	Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts & completed suicide)	Mania, incl. hypomania
Nervous System Disorders*		Headache, Dizziness, Sleep disorders, Taste disorders	Par-and Dysaesthesia, Hypoaesthesia, Tremor, Seizures (including status epilepticus Vertigo	Migraine, Disturbed coordination, Gait disturbance, Olfactory nerve disorders Intracranial hypertension & pseudo tumor cerebri)	Peripheral neuropathy and polyneuropathy
Eye Disorders*			Visual disturbances (e.g. diplopia)	Visual colour distortions	
Ear & Labyrinth Disorders*			Tinnitus, Hearing loss / Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia & torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged
Vascular Disorders			Vasodilatation, Hypotension, Syncope	Vasculitis	
Respiratory, Thoracic & Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastro-intestinal Disorders	Nausea Diarrhoea	Vomiting Gastro-intestinal & abdominal pains, Dyspepsia Flatulence	Antibiotic associated colitis (very rarely with possible fatal outcome)	Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment, Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure)	
Skin & Subcutaneous Tissue Disorders		Rash, Pruritus, Urticaria	Photosensitivity reactions	Petechiae, Erythema multiforme, Erythema nodosum, Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	Acute Generalised Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal & Connective Tissue Disorders*		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia, Arthritis Increased muscle tone and cramping	Muscular weakness, Tendinitis, Tendon rupture (predominantly Achilles tendon) Exacerbation of symptoms of myasthenia gravis	
Renal & Urinary Disorders		Renal impairment	Renal failure, Haematuria, Crystalluria, Tubulointerstitial nephritis		
General Disorders & Administration Site Conditions*		Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Increased amylase		International normalised ratio increased (in patients treated with Vitamin K antagonists)

* Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors. **Paediatric population:** The incidence of arthropathy (arthralgia, arthritis), mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly. **Adverse Laboratory Changes:** Changes in laboratory parameters are listed below: ● Hepatic: Elevations of ALT (SGPT), AST (SGOT), alkaline phosphatase, LDH, serum bilirubin. ● Hematologic–Eosinophilia, leukopenia, decreased blood platelets, elevated blood platelets, pancytopenia. ● Renal: Elevations of serum creatinine, BUN, crystalluria, cylindruria, and hematuria have been reported. ● Other changes: occurring were: elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, and leukocytosis

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.

PHARMACOLOGICAL PROPERTIES: PHARMACODYNAMICS 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 /Pharmacodynamics 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. ***Spectrum of antibacterial activity:*** Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains: ***EUCAST Recommendations:***

Microorganisms	Susceptible	Resistant
Enterobacteriaceae	S ≤ 0.5mg/L	R >1mg/L
Pseudomonas spp.	S ≤ 0.5mg/L	R >1mg/L
Acinetobacter spp.	S ≤ 1mg/L	R >1mg/L
Staphylococcus spp.†	S ≤ 1mg/L	R >1mg/L

Microorganisms	Susceptible	Resistant
Haemophilus influenzae and Moraxella catarrhalis	S ≤ 0.5mg/L	R >0.5mg/L
Neisseria gonorrhoeae	S ≤ 0.03mg/L	R >0.06mg/L
Neisseria meningitidis	S ≤ 0.03mg/L	R >0.06mg/L
Non-species-related breakpoints*	S ≤ 0.5mg/L	R >1mg/ L

● Staphylococcus spp.- breakpoints for ciprofloxacin relate to high dose therapy. ● * Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

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

Groupings of relevant species according to ciprofloxacin susceptibility (for Streptococcus species)

COMMONLY SUSCEPTIBLE SPECIES: Aerobic Gram-positive micro-organisms: *Bacillus anthracis* (1)

Aerobic Gram-negative micro-organisms: *Aeromonas spp, Brucella spp., Citrobacter koseri ,Francisella tularensis, Haemophilus ducreyi, Haemophilus influenzae*, Legionella spp., Moraxella catarrhalis*, Neisseria meningitides, Pasteurella spp., Salmonella spp.*, Shigella spp.*, Vibrio spp., Yersinia pestis.* **Anaerobic micro-organisms:** Mobiluncus **Other micro-organisms:** Chlamydia trachomatis($), Chlamydia pneumoniae ($);, Mycoplasma hominis($);, Mycoplasma pneumoniae ($):

SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM: Aerobic Gram-positive micro-organisms: Enterococcus faecalis ($) Staphylococcus spp. *(2) **Aerobic Gram-negative micro-organisms:** *Acinetobacter baumannii+, Burkholderia cepacia+*, Campylobacter spp. +*, Citrobacter freundii*, Enterobacter aerogenes, Enterobacter cloacae*, Escherichia coli*, Klebsiella oxytoca, Klebsiella pneumoniae*, Morganella morganii*, Neisseria gonorrhoeae*, Proteus mirabilis*, Proteus vulgaris*, Providencia spp., Pseudomonas aeruginosa*, Pseudomonas fluorescens, Serratia marcescens*.* **Anaerobic micro-organisms:** *Peptostreptococcus spp., Propionibacterium acnes.*

INHERENTLY RESISTANT ORGANISMS: Aerobic Gram-positive micro-organisms: *Actinomyces Enterococcus faecium, Listeria monocytogenes.* **Aerobic Gram-negative micro-organisms:** *Stenotrophomonas maltophilia.* **Anaerobic micro-organisms:** *Excepted as listed above.* **Other micro-organisms:** *Mycoplasma genitalium, Ureaplasma urealiticum.*

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

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. **Distribution:** Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached. **Biotransformation:** Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (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.

Excretion of ciprofloxacin (% of dose)		
	Oral Administration	
	Urine	Faeces
Ciprofloxacin	44.7	25,0
Metabolites (M1-M4)	11.3	7,5

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 12 h. Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients: The pharmacokinetic data in paediatric patients are limited. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

Directions for Reconstitutions: NOVIDAT® Dry Powder for Suspension 125mg/5ml & 250mg/5ml (60ml): Shake bottle to loosen the mass. Add one time completely filled provided cup (5ml) with freshly boiled cool water in to the bottle, shake well to form uniform suspension.

Appropriate Dosing Volumes of the Reconstituted Oral Suspension:

Dose	125mg/5ml	250mg/5ml
125mg	5ml	2.5ml
250mg	10ml	5ml

Dose	125mg/5ml	250mg/5ml
500mg	20ml	10ml
750mg	30ml	15ml

STABILITY: See expiry on the pack.

AVAILABILITY

NOVIDAT® 250mg tablets in a pack of 10's
NOVIDAT® 500mg tablets in a pack of 10's
NOVIDAT® dry powder for suspension (125mg/5ml) in a pack of 60ml
NOVIDAT® dry powder for suspension (250mg/5ml) in a pack of 60ml

INSTRUCTIONS

Dosage as advised by the physician. To be sold on the prescription of registered medical practitioner.
Keep out of reach of children. Avoid exposure to heat, light and humidity.
Store between 15 to 30°C. Improper storage may deteriorate the medicine.

For Tablets: Store in the original package in order to protect from moisture.

For Suspension: The reconstituted suspension should be kept at 8-15°C, so that the potency of the product remains stable and be used within 14 days of reconstitution.
Shake suspension before use.

نوویڈیٹ ٹیبلٹ / ڈرائی پاؤڈر برائے سسپینشن
(سپروفلاکساسن ہائیڈروکلورائیڈ)

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۔
برائے ٹیبلٹ: دوا کو خشک جگہ پر محفوظ رکھنے کے لیے اسکی اصل پیکنگ میں رکھیں۔
برائے سسپینشن: تیار شدہ سسپینشن کو ۸ سے ۱۵ ڈگری سینٹی گریڈ پر رکھیں تاکہ دوا کی تاثیر برقرار رہے اور ۱۴ ایام کے اندر استعمال کر لیں۔

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

R.N-11/HA/07/2020

NOVIDAT® Injection
(Ciprofloxacin)

COMPOSITION:

NOVIDAT® Injection
Each 100ml contains:
Ciprofloxacin USP 200mg

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

PROPERTIES:
Ciprofloxacin is of semi-synthetic origin and belongs to quinolone carboxylic acid. It belongs to DNA gyrase inhibitor pharmacological group, on the basis of mechanism of action and also classified in Antibiotics pharmacological group
Ciprofloxacin is effective against many gram positive and gram negative bacteria, including some strains resistant to penicillins, cyclosporins and aminoglycosides

INDICATIONS AND USAGE:
NOVIDAT® is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions and patient populations listed below:
Urinary Tract Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter diversus, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus epidermidis, Staphylococcus saprophyticus, or Enterococcus faecalis*

Acute Uncomplicated Cystitis in females caused by *Escherichia coli* or *Staphylococcus saprophyticus*

Chronic Bacterial Prostatitis caused by *Escherichia coli* or *Proteus mirabilis*

Lower Respiratory Tract Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae, or Streptococcus pneumoniae*. Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae*

Acute Sinusitis caused by *Haemophilus influenzae, Streptococcus pneumoniae*, or *Moraxella catarrhalis*

Skin and Skin Structure Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus aureus* (Methicillin-susceptible), *Staphylococcus epidermidis or Streptococcus pyogenes*

Bone and Joint Infections caused by *Enterobacter cloacae, Serratia marcescens*, or *Pseudomonas aeruginosa*

Complicated Intra-Abdominal Infections (Used in combination with metronidazole) caused by *Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumoniae, or Bacteroides fragilis*

Infectious Diarrhoea caused by *Escherichia coli* (Enterotoxigenic strains), *Campylobacter jejuni, Shigella boydii, Shigella dysenteriae, Shigella flexneri or Shigella sonnei* when antibacterial therapy is indicated

Typhoid Fever (Enteric Fever) caused by *Salmonella typhi*

NOTE: The efficacy of ciprofloxacin in the eradication of the chronic typhoid carrier state has not been demonstrated

Uncomplicated Cervical and Urethral Gonorrhoea due to *Neisseria gonorrhoeae*

Complicated Urinary Tract Infections and Pyelonephritis due to *Escherichia coli* in paediatric patients (1 to 17 years of age)

CONTRAINDICATIONS:
NOVIDAT® (Ciprofloxacin) is contraindicated in persons with a history of hypersensitivity to ciprofloxacin or any member of the quinolone class of antimicrobial agents

WARNINGS:
There is a risk of serious and occasionally fatal hypersensitivity reactions after multiple doses. Treatment should be discontinued at the first appearance of skin rash, jaundice, or any other sign of hypersensitivity, and supportive measures should be instituted
Risk of Clostridium difficile-associated diarrhoea (CDAD) should be considered

SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS
Fluoroquinolones, including (Ciprofloxacin), have been associated with disabling and potentially irreversible serious adverse reaction that have occurred together, including:
- Tendinitis and tendon rupture
- Peripheral Neuropathy
- Central nervous system effects

Discontinue (Ciprofloxacin) immediately and avoid the use of Fluoroquinolones, including (Ciprofloxacin) in patients who experience any of these serious adverse reactions
Fluoroquinolones, including (Ciprofloxacin) may exacerbate muscle weakness in patients with myasthenia gravis. Avoid (Ciprofloxacin) in patients with known history of myasthenia gravis.
As fluoroquinolones including (Ciprofloxacin) have been associated with serious adverse reactions, reserve (Ciprofloxacin) for use in patients who have no alternative treatment options for the following indications:
- Acute exacerbation of chronic bronchitis
- Acute sinusitis
- Acute uncomplicated cystitis (not for Ciprofloxacin injection and Moxifloxacin infusion and tablets)

Pregnant Women:
The safety and effectiveness of ciprofloxacin in pregnant and lactating women have not been established
Paediatrics: Ciprofloxacin should be used in paediatric patients (Less than 18 years of age) only for infections listed in the indications section. An increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues, has been observed

PRECAUTIONS:
General: **NOVIDAT®** injection should be administered by intravenous infusion over a period of 60 minutes. Local IV site reactions have been reported with the intravenous administration of ciprofloxacin. These reactions are more frequent if infusion time is 30 minutes or less or if small veins of the hand are used
In epileptics and in patients who have suffered from previous CNS-disorders (e.g. Lowered convulsion threshold, previous history of convulsions, reduced cerebral blood flow, altered brain structure or stroke), **NOVIDAT®** should only be used where the benefits of treatment exceed the risks, since these patients are endangered because of possible Central Nervous System side effects

Limitation / Restriction of use: Fluroquinolones should be reserved for use in patients who have no other treatment options available for acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI)

SIDE-EFFECTS:
The symptomatic adverse reactions produced by ciprofloxacin are more or less tolerable and if they become severe, they can be treated symptomatically, these include dizziness, headache, nausea, vomiting, diarrhoea, nervousness, tremors, rashes, urticaria, pruritus, photosensitivity, elevation of liver enzymes, eosinophilia, increased intracranial pressure and CDAD

Worsening of symptoms of Myasthenia Gravis / exacerbation of Myasthenia Gravis

Peripheral neuropathy: This serious nerve damage potentially caused by fluoroquinolones may occur soon after these drugs are taken and may be permanent. If a patient develops symptoms of peripheral neuropathy, the fluoroquinolone should be stopped, and the patient should be switched to another, non-fluoroquinolones antibacterial drug, unless the benefit of continued treatment with a fluoroquinolone outweighs the risk

DRUG INTERACTIONS:
Ciprofloxacin is known to interact with other drugs like aluminium hydroxide and oxide, azlocillin (Na), caffeine, calcium carbonate, chloramphenicol, cyclosporin A, diazepam, foscarnet (Na), rifampicin, sucralfate, theophylline, warfarin (Na), alprazolam, bromazepam, zinc sulphate, zolmitriptan, zolpidem (Tartrate), estazolam, ropinirole (HCl). These interactions are sometimes beneficial and sometimes may pose threats to life. Always consult your physician for the change of dose regimen or an alternative drug of choice that may strictly be required. Ciprofloxacin should not be taken with dairy products (Like milk or yogurt or calcium fortified juices alone)

DOSAGE:
Unless otherwise prescribed, the following guideline doses are recommended:

Respiratory tract infections
- According to severity and organism.....200mg-400mg

Urinary tract infections
- Acute uncomplicated..... 200mg
- Cystitis in women (Before menopause).....single dose 200mg
- Complicated .....single dose 200mg

Gonorrhoea
- Extragenital 200mg
- Acute, uncomplicated .....single dose 200mg

Diarrhoea .....2 x 200mg

* Particularly severe, life threatening infections, i.e. ..... 3 x 400mg
- Streptococcal pneumonia
- Recurrent infections in cystic fibrosis
- Bone and joint infections
- Septicemia
- Peritonitis (In particular when Pseudomonas, Staphylococcus or Streptococcus is present)

Usual duration of treatment is 7-14 days
After intravenous administration the treatment can be continued orally
Elderly people should receive a dose as low as possible depending on the severity of their illness and the creatinine clearance
Administration: (Intravenous administration)
NOVIDAT® injection should be administered to adults by intravenous infusion over a period of 60 minutes
The infusion solution can be infused either directly or after mixing with other infusion solutions
Important compatibilities:
Unless compatibility with other infusion solutions/drugs has been confirmed, the infusion solution must always be administered separately
Duration of Use:
Duration of treatment depends on severity of the illness and on the clinical and biological course

PRESENTATION:
NOVIDAT® injection 200mg in a pack of 100ml
NOVIDAT® DS injection 400mg in a pack of 100ml

STABILITY:
See expiry on the pack

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

Caution:Injection should not be used if container is leaking, solution is cloudy or it contains undissolved particle(s)

نوویڈیٹ انجکشن
(سپرو فلوکساسن)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں
بچوں کی پہنچ سے دور رکھیں
دوا کو دھوپ، گرمی اور منجمد ہونے سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی
تنبیہ: انجکشن کے لیک ہونے، دُھندلا ہونے یا اس میں کوئی غیر حل پزیر شے نظر آنے کی صورت میں ہرگز استعمال نہ کریں

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com

NOVIDAT® XR
(Ciprofloxacin) XR Tablets

DESCRIPTION:

NOVIDAT® XR contains ciprofloxacin, a synthetic broad-spectrum antimicrobial agent for oral administration. Chemically, it is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its molecular formula is $C_{17}H_{18}FN_3O_3$

COMPOSITION:

NOVIDAT® XR 500mg Tablets

Each extended release film coated tablet contains:

Ciprofloxacin USP 500mg

NOVIDAT® XR 1000mg Tablets

Each extended release film coated tablet contains:

Ciprofloxacin USP 1000mg

INDICATIONS AND USAGE:

NOVIDAT® XR is indicated for the treatment of urinary tract infections including acute uncomplicated pyelonephritis, caused by susceptible strains of the designated microorganisms. **NOVIDAT® XR** and ciprofloxacin immediate-release tablets are not interchangeable. Uncomplicated urinary tract infections (acute cystitis) caused by *Escherichia coli*, *Proteus mirabilis*, *Enterococcus faecalis*, *or Staphylococcus saprophyticus*. Complicated urinary tract infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Proteus mirabilis or Pseudomonas aeruginosa*. Acute uncomplicated pyelonephritis caused by *Escherichia coli*

PHARMACOKINETICS:

Absorption

NOVIDAT® XR tablets are formulated to release drug at a slower rate compared to immediate-release tablets. Approximately 35% of the dose is contained within an immediate-release component, while the remaining 65% is contained in a slow-release matrix. Maximum plasma ciprofloxacin concentration is attained between 1 and 4 hours after dosing with **NOVIDAT® XR**. In comparison to the 250mg and 500mg ciprofloxacin immediate-release b.i.d. treatment, the C_{max} of **NOVIDAT® XR** 500mg and 1000mg once daily are higher than the corresponding b.i.d. doses, while the AUCs over 24 hours are equivalent

Pharmacokinetic Comparison

Dose	C_{max} (mg/l)	$AUC_{0\text{-}24hrs.}$ (mg·h/l)	$T_{1/2}$ (hr)	T_{max} (hr)*
NOVIDAT® XR 500mg q.d.	1.59 ± 0.43	7.97 ± 1.87	6.6 ± 1.4	1.5 (1-2.5)
NOVIDAT® 250mg b.i.d.	1.14 ± 0.23	8.25 ± 2.15	4.8 ± 0.6	1 (0.5-2.5)
NOVIDAT® XR 1000mg q.d.	3.11 ± 1.08	16.83 ± 5.65	6.31 ± 0.72	2 (1-4)
NOVIDAT® 500mg b.i.d.	2.06 ± 0.41	17.04 ± 4.79	5.66 ± 0.89	2 (0.5-3.5)

* Median (range)

Distribution

The volume of distribution calculated for intravenous ciprofloxacin is approximately 2.1 – 2.7 L/kg. The binding of ciprofloxacin to serum proteins is 20% to 40%, which is not likely to be high enough to cause significant protein binding interactions with other drugs

Metabolism

Four metabolites of ciprofloxacin were identified in human urine. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin

Elimination

Approximately 35% of an orally administered dose of **NOVIDAT® XR** is excreted in the urine as an unchanged drug. The urinary excretion of ciprofloxacin is almost complete within 24 hrs. after dosing. The renal clearance of ciprofloxacin, which is approximately 300ml/minute, exceeds the normal glomerular filtration rate of 120ml/minute. Only a small amount of the dose administered is recovered from the bile as an unchanged drug. An additional 1% to 2% of the dose is recovered from the bile in the form of metabolite

DOSAGE GUIDELINES:

Indication	Unit Dose	Frequency	Usual Dose
Uncomplicated urinary tract Infection (acute cystitis)	500mg	q 24 h	3 Days
Complicated urinary tract infection	1000mg	q 24 h	7-14 Days
Acute uncomplicated pyelonephritis	1000mg	q 24 h	7-14 Days

OR
As directed by the physician

SPECIAL POPULATION:

Impaired Renal Function

No dose adjustment is required for patients with uncomplicated urinary tract infections receiving 500mg **NOVIDAT® XR**. For complicated urinary tract infection and acute uncomplicated pyelonephritis, where 1000mg is the appropriate dose, the dosage of **NOVIDAT® XR** should be reduced to **NOVIDAT® XR** 500mg q 24 h in patients with creatinine clearance below 30ml/min.

OVERDOSAGE:

In the event of acute excessive over dosage, reversible renal toxicity has been reported in some cases. The stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment including monitoring of renal function and administration of magnesium or calcium containing antacids which can reduce the absorption of ciprofloxacin

CONTRAINDICATIONS:

Ciprofloxacin is contraindicated:

• In persons with a history of hypersensitivity to ciprofloxacin, any member of the quinolone class of antimicrobial agents or any of the product components

• Concomitant administration with tizanidine

Limitation / Restriction of use: Fluroquinolones should be reserved for use in patients who have no other treatment options available for acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI)

WARNINGS:

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

Fluoroquinolones, including (Ciprofloxacin), have been associated with disabling and potentially irreversible serious adverse reaction that have occurred together, including:

- Tendinitis and tendon rupture
- Peripheral Neuropathy
- Central nervous system effects

Discontinue (Ciprofloxacin) immediately and avoid the use of Fluoroquinolones, including (Ciprofloxacin) in patients who experience any of these serious adverse reactions

Fluoroquinolones, including (Ciprofloxacin) may exacerbate muscle weakness in patients with myasthenia gravis. Avoid (Ciprofloxacin) in patients with known history of myasthenia gravis

As fluoroquinolones including (Ciprofloxacin) have been associated with serious adverse reactions, reserve (Ciprofloxacin) for use in patients who have no alternative treatment options for the following indications:

- Acute exacerbation of chronic bronchitis
- Acute sinusitis
- Acute uncomplicated cystitis (not for Ciprofloxacin injection and Moxifloxacin infusion and tablets)

ADVERSE REACTIONS:

The most common adverse reactions are nausea, vomiting, dizziness, headache, diarrhoea, dyspepsia, vaginal moniliasis. Additional uncommon events that occurred in less than 1% of ciprofloxacin extended release treated patients are: *Abdominal pain, asthenia, malaise, photosensitivity reaction, bradycardia, migraine, syncope, anorexia, constipation, dry mouth, flatulence, liver function tests abnormal, thirst, prothrombin decrease, abnormal dreams, depersonalization, depression, hypertonia, incoordination, insomnia, somnolence, tremor, vertigo, hyperglycemia, dry skin, maculopapular rash, photosensitivity/phototoxicity reactions, pruritus, rash, skin disorder, urticaria, vesiculobullous rash, diplopia, taste perversion, dysmenorrhea, hematuria, kidney function abnormal and vaginitis*

Worsening of symptoms of Myasthenia Gravis / exacerbation of Myasthenia Gravis

DRUG INTERACTION:

Ciprofloxacin is known to interact with other drugs like theophylline, caffeine, multivalent cation-containing products such as magnesium/aluminum antacids or products containing calcium, iron, or zinc. **NOVIDAT® XR** should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as metal cations such as iron and multivitamin preparations with zinc

STABILITY:

See expiry on the pack

PRESENTATION:

NOVIDAT® XR 500mg tablets in a pack of 2 x 5's

NOVIDAT® XR 1000mg tablets in a pack of 2 x 5's

INSTRUCTIONS:

Keep out of reach of children

Avoid exposure to heat, light and humidity

Store between 15 to 30°C

Improper storage may deteriorate the medicine

نووِیڈیٹ ایکس آر ٹیبلٹ

(سِپروفلاکسِن)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال 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

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com