BRAND NAME:	**NARAFLOX**
GENERIC NAME:	**LEVOFLOXACIN TABLETS 500 MG**

1.3 PRODUCT INFORMATION

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

Enclosed

BRAND NAME:	**NARAFLOX**
GENERIC NAME:	**LEVOFLOXACIN TABLETS 500 MG**

1. Name of drug product

NARAFLOX

1.1 (Trade) name of product

NARAFLOX

(Levofloxacin Tablets 500 mg)

1.2 Strength

Levofloxacin Hemihydrate USP 500 mg

1.3 Pharmaceutical Dosage Form

Solid Oral dosage form **(**Tablets)

2. QUALITATIVE & QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Each Film coated Tablet Contains:

Levofloxacin Hemihydrate

Equivalent to Levofloxacin ……500 mg

Excipients ……..…….q.s.

Colour: Ponceau 4R

MAXHEAL
For Maximum Healing

BRAND NAME:	**NARAFLOX**
GENERIC NAME:	**LEVOFLOXACIN TABLETS 500 MG**

Batch Formula:

Batch Size: 4, 40, 000 Tablets (369.600 Kg)

Sr. No.	Ingredients	Spec.	Unit Formula (mg)	Batch Formula (kg)
Granulation				
Dry Mixing				
1	LevofloxacinHemihydrate Eq. to Levofloxacin	USP	512.500	225.500*
2	Microcrystalline Cellulose	BP	150.000	66.000**
3	Lactose	IH	96.000	42.240
4	Carmellose Sodium	BP	5.000	2.200
5	Sodium Lauryl Sulfate	BP	2.000	0.880
6	Crosspovidone	USP	5.000	2.200
Binder				
7	PVP K-30	BP	1.500	0.660
8	Maize Starch	BP	5.000	2.200
9	Purified water	IH	q.s.	83.000
Lubrication				
10	Purified Talc	BP	6.000	2.640
11	Carmellose Sodium	BP	25.000	11.000
12	Crosspovidone	USP	5.000	2.200
13	Colloidal Anhydrous Silica (Aerosil)	BP	4.000	1.760
14	Magnesium Stearate	BP	3.000	1.320
Weigh of Compressed Tablet			**820.000**	**360.800 kg**
Coating				
15	Insta Coat Universal (IC-U-1308) (White)	IH	16.700	7.348
16	Ponceau 4R	IH	3.300	1.452
17	Purified water	IH	q.s.	65.120
Weigh of Coated Tablet			**840.000**	**369.600 kg**

Remark:

* Quantity of Levofloxacin Hemihydrate is taken after calculation based on assay.

** Microcrystalline cellulose quantity change according to change in quantity of Levofloxacin Hemihydrate.

3. PHARMACEUTICAL DOSAGE FORM

Tablets

Red coloured, Caplet shaped film coated tablets, plain on both the side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In adults, Tablets are indicated for the treatment of the following infections:

• Acute bacterial sinusitis

In above-mentioned infections, Tablets product should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections

• Community-acquired pneumonia

• Complicated skin and soft tissue infections / Complicated skin and skin structure infection. For the above-mentioned infections, Naraflox Tablets should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the treatment of these infections.

• Acute pyelonephritis and complicated urinary tract infections (see section 4.4)

• Chronic bacterial prostatitis

• Uncomplicated cystitis (see section 4.4)

In above-mentioned infections, Naraflox Tablets product should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections

• Inhalation Anthrax: postexposure prophylaxis and curative treatment (see section 4.4)

• Acute exacerbation of chronic obstructive pulmonary disease including bronchitis.

In above-mentioned infections, Naraflox Tablets product should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections

Tablets may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous levofloxacin. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

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4.2 Posology and method of administration

NARAFLOX Tablets are administered once or twice daily. The dosage depends on the type and severity of the infection and the sensitivity of the presumed causative pathogen.

Naraflox Tablets may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous levofloxacin; given the bioequivalence of the parenteral and oral forms, the same dosage can be used.

Posology

The following dose recommendations can be given for Levofloxacin:

Dosage in patients with normal renal function (creatinine clearance > 50ml / min)

Indication	**Daily dose regimen (according to severity)**	**Duration of treatment**
Acute bacterial sinusitis	500 mg once daily	10 -14 days
Acute bacterial exacerbations of chronic bronchitis	500 mg once daily	7 – 10 days
Community-acquired pneumonia	500 mg once or twice daily	7 – 14 days
Pyelonephritis	500 mg once daily	7-10 days
Uncomplicated cystitis	250 mg once daily	3 days
Complicated urinary tract infections	500 mg once daily	7 – 14 days
Chronic bacterial prostatitis	500 mg once daily	28 days
Complicated Skin and soft tissue infections	500mg once or twice daily	7 – 14 days
Inhalation Anthrax	500 mg once daily	8 weeks

Special populations

Impaired renal function (creatinine clearance ≤50 ml / min).

	Dose regimen		
	250 mg / 24 h	**500 mg / 24 h**	**500 mg /12 h**
Creatinine clearance	*first dose: 250 mg*	*first* dose : 500 mg	*first* dose : 500 mg
50-20 ml / min	*then* : 125 mg / 24 h	*then :* 250 mg / 24 h	*then :* 250 mg / 12 h
19 – 10 ml / min	*then* : 125 mg / 48 h	*then :* 125 mg / 24 h	*then :* 125 mg / 12 h
< 10 ml / min (including haemodialysis and 1 CAPD	*then* : 125 mg / 48 h	*then :* 125 mg / 24 h	*then :* 125 mg / 24 h

1 No additional doses are required after haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

Impaired liver function

No adjustment of dosage is required since levofloxacin is not metabolised to any relevant extent by the liver and is mainly excreted by the kidneys.

Elderly Population

No adjustment of dosage is required in the elderly, other than that imposed by consideration of renal function. (also see section 4.4 regarding QT interval prolongation).

Paediatric population

Levofloxacin is contraindicated in children and growing adolescents (less than 18 years of age) (see section 4.3).

Method of administration

For oral use.

4.3 Contraindications

Levofloxacin 500mg film-coated tablets must not be used:

- In patients hypersensitive to levofloxacin or other quinolones or to any of the excipients listed in section 6.1
- In patients with epilepsy,
- In patients with history of tendon disorders related to fluoroquinolone administration,
- In children or growing adolescents,
- During pregnancy,
- In breast-feeding women.

4.4 Special warnings and precautions for use

The use of Naraflox Tablets should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with Naraflox Tablets should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3).

Aortic aneurysm and dissection, and heart valve regurgitation/incompetence

Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake of fluoroquinolones, Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.8).

Therefore, fluoroquinolones should only be used after 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 aortic both aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or vascular Ehlers-Danlos syndrome, Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis).
- 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.

Methicillin-resistant Staphylococcus aureus (MRSA)

Methicillin- resistant S. Aureus are very likely to possess co- resistance to flouroquinolones, including levofloxacin. Therefore levofloxacin is not recommended for the treatment of known or suspected MRSA infections unless laboratory results have confirmed susceptibility of the organism to levofloxacin (and commonly recommended antibacterial agents for the treatment of MRSA-infections are considered inappropriate).

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Levofloxacin may be used in the treatment of Acute Bacterial Sinusitis and Acute Exacerbation of Chronic Bronchitis when these infections have been adequately diagnosed.

Resistance to fluoroquinolones of E. 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 E. coli to fluoroquinolones.

Inhalation Anthrax: Use in humans is based on in vitro Bacillus anthracis 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.

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. Levofloxacin Tablet should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice

Tendinitis and tendon rupture

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with levofloxacin and have been reported up to several months after discontinuation of treatment in patients receiving daily doses of 1000 mg levofloxacin. The risk of tendonitis 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). treatment with Levofloxacin tablet 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.

Clostridium difficile-associated disease

Diarrhoea, particularly if severe, persistent and / or bloody, during or after treatment with

NARAFLOX Tablets (including several weeks after treatment), may be symptomatic of Clostridium difficile-associated disease (CDAD), the most severe form of which is pseudomembranous colitis (see section 4.8). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis (see section 4.8). It is therefore important to consider this diagnosis in patients who develop serious diarrhoea during or after treatment with levofloxacin. If CDAD is suspected or confirmed, Naraflox Tablets must be stopped immediately and patients should be treated with supportive measure ± specific therapy without delay (e.g. oral vancomycin). Products inhibiting the peristalsis are contraindicated in this clinical situation.

Patients predisposed to seizures

Quinolones may lower the seizure threshold and may trigger seizures. Naraflox Tablets are contraindicated in patients with a history of epilepsy (see section 4.3) and, as with other quinolones, should be used with extreme caution in patients predisposed to, or concomitant treatment with drugs which lower the cerebral seizure threshold, such as theophylline (see section 4.5). In case of convulsive seizures, treatment with levofloxacin should be discontinued.

Patients with G-6-phosphate dehydrogenase deficiency

Patients with latent or actual defects in glucose-6-phospahte dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents, and so levofloxacin should be used with caution. Therefore, if levofloxacin has to be used in these patients, potential occurrence of haemolysis should be monitored.

Patients with renal impairment

Since levofloxacin is excreted mainly by the kidneys, the dose of Naraflox Tablets should be adjusted in patients with renal impairment (see section 4.2).

Hypersensitivity reactions

Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema up to anaphylactic shock), occasionally following the initial dose (see section 4.8). Patients should discontinue treatment immediately and contact their physician or an emergency physician, who will initiate appropriate emergency measures.

Severe bullous reactions

Cases of severe bullous skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with levofloxacin (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Dysglycemia

As with all quinolones, disturbances in blood glucose, including both hypoglycemia and hyperglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., libenclamide) or with insulin. In these diabetic patients, careful monitoring of blood glucose is recommended. (See section 4.8).

Prevention of photosensitisation

Although photosensitisation is very rare with levofloxacin, it is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), during treatment and for 48 hours following treatment discontinuation in order to prevent photosensitisation.

Patients treated with Vitamin K antagonists

Due to possible increase in coagulation tests (PT / INR) and / or bleeding in patients treated with Naraflox Tablets in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomitantly (see section 4.5).

Psychotic reactions

Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin. In very rare cases these have progressed to suicidal thoughts and self-endangering behaviour-sometimes after only a single dose of levofloxacin (see section 4.8). In the event that the patient develops these reactions, levofloxacin should be discontinued and appropriate measures instituted. Caution is recommended if levofloxacin is to be used in psychotic patients or in patients with history of psychiatric disease.

Cardiac disorders

QT interval prolongation

Caution should be taken when using fluoroquinolones, including levofloxacin, 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 antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

• Uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)

• Elderly patients and women may be more sensitive to QTc-prolonging medications.

• Therefore, caution should be taken when using fluoroquinolones, including levofloxacin, in these populations.

• Cardiac disease (e.g. heart failure, myocardial infarction, bradycardia) (See section 4.2 Elderly Population, 4.5, 4.8, 4.9).

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving fluoroquinolones.Patients under treatment with Naraflox Tablets should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition. (see section 4.8)

Hepatobiliary disorders

Cases of hepatic necrosis up to life threatening hepatic failure have been reported with levofloxacin, primarily in patients with severe underlying diseases, e.g. sepsis (see section 4.8). Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

Exacerbation of myasthenia gravis

Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Postmarketing serious adverse reactions, including deaths and the requirement for respiratory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Levofloxacin is not recommended in

patients with a known history of myasthenia gravis.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see sections 4.7 and 4.8).

Super infection

The use of levofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms. If super infection occurs during therapy, appropriate measures should be taken.

Interference with laboratory tests

In patients treated with levofloxacin, determination of opiates in urine may give false-positive results. It may be necessary to confirm positive opiate screens by more specific method. Levofloxacin may inhibit the growth of Mycobacterium tuberculosis and, therefore, may give false-negative results in the bacteriological diagnosis of tuberculosis.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on Levofloxacin Tablets:

Iron salts, magnesium – or aluminium –containing antacids, didanosine

Levofloxacin absorption is significantly reduced when iron salts, or magnesium-or aluminium-containing antacids, or didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents) are administered concomitantly with Naraflox Tablets. Concurrent administration of fluoroquinolones with multi-vitamins containing zinc appears to reduce their oral absorption. It is recommended that preparations containing divalent or trivalent cations such as iron salts, zinc salts or magnesium-or aluminium-containing antacids or didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents) should not be taken 2 hours before or after Levofloxacin tablet administration (see section 4.2).

Calcium salts have a minimal effect on the oral absorption of levofloxacin.

Sucralfate

The bioavailability of Naraflox Tablets is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and Levofloxacin, it is best to administer sucralfate 2 hours after the Levofloxacin tablet administration (see section 4.2).

Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs

No pharmacokinetic interactions of levofloxacin were found with theophylline in a clinical study. However a pronounced lowering of the cerebral seizure threshold may occur when quinolones are given concurrently with theophylline, non-steroidal anti-inflammatory drugs, or other agents which lower the seizure threshold.

Levofloxacin concentrations were about 13% higher in the presence of fenbufen than when administered alone.

Probenecid and cimetidine

Probenecid and cimetidine had a statistically significant effect on the elimination of levofloxacin. The renal clearance of levofloxacin was reduced by cimetidine (24%) and probenecid (34%). This is because both drugs are capable of blocking the renal tubular secretion of levofloxacin. However, at the tested doses in the study, the statistically significant kinetic differences are unlikely to be of clinical relevance.

Caution should be exercised when levofloxacin is coadministered with drugs that effect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

Other relevant information

Clinical pharmacology studies have shown that the pharmacokinetics of levofloxacin were not affected to any clinically relevant extent when levofloxacin was administered together with the following drugs: calcium carbonate, digoxin, glibenclamide, ranitidine.

Effect of Levofloxacin Tablets on other medicinal products

Ciclosporin

The half-life of ciclosprorin was increased by 33% when coadministered with levofloxacin.

Vitamin K antagonists

Increased coagulation tests (PT/INR) and / or bleeding, which may be severe, have been reported in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin). Coagulation tests, therefore, should be monitored in patients treated with vitamin K antagonists (see section 4.4)

Drugs known to prolong QT interval

Levofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs

known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics). (See section 4.4 QT interval prolongation).

Other relevant information

In a pharmacokinetic interaction study, levofloxacin did not affect the pharmacokinetics of theophylline (which is a probe substrate for CYP1A2), indicating that levofloxacin is not a CYP1A2 inhibitor.

Other forms of interactions

Food

There is no clinically relevant interaction with food. Naraflox Tablets may therefore be administered regardless of food intake.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of levofloxacin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). However in the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, Naraflox Tablets must not be used in pregnant women (see sections 4.3 and 5.3)

Breast-feeding

Levofloxacin is contraindicated in breast-feeding women. There is insufficient information on the excretion of levofloxacin in human milk; however other fluoroquinolones are excreted in breast milk. In the absence of human data and due to the experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, NarafloxTablets must not be used in breast-feeding women (see sections 4.3 and 5.3)

Fertility

Levofloxacin caused no impairment of fertility or reproductive performance in rats.

4.7 Effects on ability to drive and use machines

Certain undesirable effects (e.g. dizziness / vertigo, drowsiness, visual disturbances) may impair the patient's ability to concentrate and react, and therefore may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

4.8 Undesirable effects

The information given below is based on data from clinical studies in more than 8300 patients and on extensive post marketing experience.

The adverse reactions are described according to the MedDRA system organ class below. Frequencies are defined using the following convention: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, ≤1/100), rare (≥1/10000, ≤1/1000), very rare (≤1/10000), not known (cannot be estimated from the available data).

System organ Class	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Not known (cannot be estimated from available data)**
Infections and infestations		Fungal infection including Candida infection Pathogen resistance		
Blood and Lymphatic system disorder		Leukopenia Eosinophilia	Thrombocytopenia Neutropenia	Pancytopenia Haemolytic Anaemia, Agranulocytosis
Immune system disorders			Angioedema Hypersensitivity (see section 4.4)	Anaphylactic A shock Anaphylactoid A shock (see section 4.4)
Metabolism and nutrition disorders		Anorexia	Hypoglycaemia particularly in diabetic patients (see section 4.4)	Hyperglycaemia Hypoglycaemic coma (see section 4.4)
Psychiatric Disorders*	Insomnia	Anxiety Confusional state Nervousness	Psychotic reactions (with e.g. hallucination, paranoia) Depression	Psychotic disorders with self- endangering behaviour including suicidal ideation or suicide attempt (see

			Agitation Abnormal dreams Nightmares	section 4.4)
Nervous system Disorders*	Headache Dizziness	Somnolence Tremor Dysgeusia	Paraesthesia Convulsion (see sections 4.3 and 4.4)	Peripheral sensory neuropathy (see section 4.4) Peripheral sensory motor neuropathy (see section 4.4) Parosmia including anosmia Dyskinesia Extrapyramidal disorder Ageusia Syncope Benign intracranial hypertension
Eye disorders*			Visual disturbances such as blurred vision (see section 4.4)	Transient vision loss (see section 4.4)
Ear and Labyrinth disorders*		Vertigo	Tinnitus	Hearing loss Hearing impaired
Cardiac Disorders**			Tachycardia, Palpitation	Ventricular tachycardia, which may result in cardiac arrest Ventricular arrhythmia and torsade de pointes (reported predominantly in patients with risk factors of QT prolongation), electrocardiogram QT prolonged (see sections 4.4 and 4.9)
Vascular Disorders**			Hypotension	
Respiratory, thoracic and mediastinal disorders		Dyspnoea		Bronchospasm Pneumonitis allergic
Gastro-intestinal disorders	Diarrhoea Vomiting Nausea	Abdominal pain Dyspepsia Flatulence Constipation		Pancreatitis Diarrhoea – haemorrhagic which in very rare cases may be

				indicative of enterocolitis, including pseudomembranous colitis (see section 4.4)
Hepatobiliary disorders	Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)	Blood bilirubin increased		Jaundice and severe liver injury, including cases with fatal acute liver failure, primarily in patients with severe underlying diseases (see section 4.4) Hepatitis
Skin and subcutaneous tissue disorders b		Rash Pruritus Urticaria Hyperhidrosis		Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Photosensitivity reaction (see section 4.4) Leukocytoclastic vasculitis Stomatitis
Musculoskeletal and connective tissue disorders*		Arthralgia Myalgia	Tendon disorders (see sections 4.3 and 4.4) including tendinitis (e.g. Achilles tendon) Muscular weakness which may be of special importance in patients with myasthenia gravis (see section 4.4)	Rhabdomyolysis Tendon rupture (e.g. Achilles tendon) (see sections 4.3 and 4.4) Ligament rupture Muscle rupture Arthritis
Renal and Urinary disorders		Blood creatinine increased	Renal failure acute (e.g. due to interstitial nephritis)	
General disorders and administration site conditions*		Asthenia	Pyrexia	Pain (including pain in back, chest, and extremities)

A Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose

B Mucocutaneous reactions may sometimes occur even after the first dose

Other undesirable effects which have been associated with fluoroquinolone administration include:

- Attacks of porphyria in patients with porphyria

* Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see Section 4.4).

4.9 Overdose

According to toxicity studies in animals or clinical pharmacology studies performed with supra-therapeutic doses, the most important signs to be expected following acute overdosage of Naraflox Tablets are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval as well as gastro- intestinal reactions such as nausea and mucosal erosions.

CNS effects including confusional state, convulsion, hallucination, and tremor have been observed in post marketing experience.

In the event of overdose, symptomatic treatment should be implemented, ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Antacids may be used for protection of gastric mucosa. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body. No specific antidote exists.

5.0 Pharmacological properties

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Quinolone antibacterials - Fluroquinolone, **ATC Code:** J01MA12.

Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S (-) enantiomer of the racemic drug substance ofloxacin.

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Mechanism of action

As a fluoroquinolone antibacterial agent, levofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV.

PK/PD relationship

The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum concentration in serum (Cmax) or the area under the curve (AUC) and the minimal inhibitory concentration (MIC).

Mechanism of resistance

Resistance to levofloxacin is acquired through a stepwise process by target site mutations in both type II topoisomerases, DNA gyrase and topoisomerase IV. Other resistance mechanisms such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may also affect susceptibility to levofloxacin.

Cross-resistance between levofloxacin and other fluoroquinolones is observed. Due to the mechanism of action, there is generally no cross-resistance between levofloxacin and other classes of antibacterial agents**.**

Breakpoints

The EUCAST recommended MIC breakpoints for levofloxacin, separating susceptible from intermediately susceptible organisms and intermediately susceptible from resistant organisms are presented in the below table for MIC testing (mg/L).

EUCAST clinical MIC breakpoints for levofloxacin (version 2.0, 2012-01-01)

Pathogen	**Susceptible**	**Resistant**
Enterobacteriacae	≤ 1 mg/L	>2 mg/L
Pseudomonas spp.	≤ 1 mg/L	>2 mg/L
Acinetobacter spp.	≤ 1 mg/L	>2 mg/L
Staphylococcus spp.	≤ 1 mg/L	>2 mg/L
S.pneumoniae[1]	≤ 2 mg/L	>2 mg/L
Streptococcus A,B,C,G	≤ 1 mg/L	>2 mg/L
H.influenzae [2,3] *M.catarrhalis* [3]	≤ 1 mg/L	>1 mg/L
Non-species related breakpoints[4]	≤ 1 mg/L	>2 mg/L

1. The breakpoints for levofloxacin relate to high dose therapy.

2. Low-level fluoroquinolone resistance (ciprofloxacin MICs of 0.12-0.5 mg/l) may occur but there is no evidence that this resistance is of clinical importance in respiratory tract infections with *H. influenzae*.

3. Strains with MIC values above the susceptible breakpoint are very rare or not yet reported.

The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate must be sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant.

4. Breakpoints apply to an oral dose of 500 mg x 1 to 500 mg x 2 and an intravenous dose of 500 mg x 1 to 500 mg x 2.

Antibacterial spectrum

The prevalence of 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.

Commonly susceptible species

Aerobic Gram-positive bacteria

Bacillusanthracis

Staphylococcus aureus methi-S

Staphylococcus saprophyticus

Streptococci, group C and G

Streptococcus agalactiae

Streptococcus pneumoniae

Streptococcus pyogenes

Aerobic Gram- negative bacteria

Eikenellacorrodens

Haemophilusinfluenzae

Haemophilus para-influenzae

Klebsiella oxytoca

Moraxellacatarrhalis

Pasteurellamultocida

Proteusvulgaris

Providencia rettgeri

Anaerobic bacteria

Peptostreptococcus

Other

Chlamydophila pneumoniae

Chlamydophilapsittaci

Chlamydiatrachomatis

Legionella pneumophila

Mycoplasma pneumoniae

Mycoplasma hominis Ureaplasma urealyticum

Species for which acquired resistance may be a problem

Aerobic Gram-positive bacteria

Enterococcus faecalis

Staphylococcus aureus methicillin –resistant#

Staphylococcus coagulase negative spp

Aerobic Gram- negative bacteria

Acinetobacter baumannii

Citrobacterfreundii

Enterobacteraerogenes

Klebsiellapneumoniae

Enterobactercloacae

Escherichiacoli

Morganellamorganii

Proteusmirabilis

Providenciastuartii

Pseudomonas aeruginosa

Serratia marcescens

Anaerobic bacteria

Bacteroides fragilis

Inherently Resistant Strains

Aerobic Gram-positive bacteria

Enterococcus faecium

Methicillin-resistant S. Aureus are very likely to possess co-resistance to fluoroquinolones

5.2 Pharmacokinetic properties

Absorption

Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1-2 hr. The absolute bioavailability is approximately 99-100%.

Food has little effect on the absorption of levofloxacin.

Steady state conditions are reached within 48 hours following a 500 mg once or twice daily dosage regimen.

Distribution

Approximately 30 – 40 % of levofloxacin is bound to serum protein.

The mean volume of distribution of levofloxacin is approximately 100 l after single and repeated 500 mg doses, indicating widespread distribution into body tissues.

Penetration into tissues and body fluids:

Levofloxacin has been shown to penetrate into in bronchial mucosa, epithelial lining fluid, alveolar macrophages, lung tissue, skin (blister fluid), prostatic tissue and urine. However, levofloxacin has poor penetration intro cerebro-spinal fluid.

Biotransformation

Levofloxacin is metabolised to a very small extent, the metabolites being desmethyl-levofloxacin and levofloxacin N-oxide. These metabolites account for < 5 % of the dose excreted in urine. Levofloxacin is stereochemically stable and does not undergo chiral inversion.

Elimination

Following oral and intravenous administration of levofloxacin, it is eliminated relatively slowly from the plasma (t1/2 : 6 – 8 h). Excretion is primarily by the renal route > 85 % of the administered dose).

The mean apparent total body clearance of levofloxacin following a 500 mg single dose was 175 +/- 29.2 ml/min.

There are no major differences in the pharmacokinetics of levofloxacin following intravenous and oral administration, suggesting that the oral and intravenous routes are interchangeable.

Linearity

Levofloxacin obeys linear pharmacokinetics over a range of 50 to1000mg.

Special populations

Subjects with renal impairment

The pharmacokinetics of levofloxacin are affected by renal impairment. With decreasing renal function renal elimination and clearance are decreased, and elimination half-lives increased as shown in the table below:

Pharmacokinetics in renal insufficiency following single oral 500mg dose

Cl_{cr}[ml/min]	< 20	20 – 49	50 – 80
Cl_R [ml/min]	13	26	57
$t_{1/2}$[h]	35	27	9

Elderly subjects

There are no significant differences in levofloxacin kinetics between young and elderly subjects, except those associated with differences in creatinine clearance.

Gender differences

Separate analysis for male and female subjects showed small to marginal gender differences in levofloxacin pharmacokinetics. There is no evidence that these gender differences are of clinical relevance.

Pharmacokinetics in special patient groups

Elderly

Healthy, elderly volunteers (65 years or over) had a reduced clearance of sildenafil, resulting in approximately 90% higher plasma concentrations of sildenafil and the active N-desmethyl metabolite compared to those seen in healthy younger volunteers (18-45 years). Due to age-differences in plasma protein binding, the corresponding increase in free sildenafil plasma concentration was approximately 40%.

Renal insufficiency

In volunteers with mild to moderate renal impairment (creatinine clearance = 30-80 mL/min), the pharmacokinetics of sildenafil were not altered after receiving a 50 mg single oral dose. The mean AUC and Cmax of the N-desmethyl metabolite increased up to 126% and up to 73% respectively, compared to age-matched volunteers with no renal impairment. However, due to high inter-subject variability, these differences were not statistically significant. In volunteers with severe renal impairment (creatinine clearance <30 mL/min), sildenafil clearance was reduced, resulting in mean increases in AUC and Cmax of 100% and 88% respectively compared to age-matched volunteers with no renal impairment. In addition, N-desmethyl metabolite AUC and Cmax values were significantly increased by 200% and 79% respectively.

Hepatic insufficiency

In volunteers with mild to moderate hepatic cirrhosis (Child-Pugh A and B) sildenafil clearance was reduced, resulting in increases in AUC (84%) and Cmax (47%) compared to age-matched volunteers with no hepatic impairment. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function have not been studied.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential and toxicity to reproduction and development.

Levofloxacin caused no impairment of fertility or reproductive performance in rats and its only effect on fetuses was delayed maturation as a result of maternal toxicity.

Levofloxacin did not induce gene mutations in bacterial or mammalian cells but did induce chromosome aberrations in Chinese hamster lung cells in vitro. These effects can be attributed to inhibition of topoisomerase II. In vivo tests (micronucleus, sister chromatid exchange, unscheduled DNA synthesis, dominant lethal tests) did not show any genotoxic potential.

Studies in the mouse showed levofloxacin to have phototoxic activity only at very high doses. Levofloxacin did not show any genotoxic potential in a photomutagenicity assay, and it reduced tumour development in a photocarcinogenity study.

In common with other fluoroquinolones, levofloxacin showed effects on cartilage (blistering and cavities) in rats and dogs. These findings were more marked in young animals.

6. Pharmaceutical Particulars

6.1. List of excipients

Microcrystalline Cellulose, Lactose, Carmellose Sodium, Sodium Lauryl Sulfate, Crosspovidone, PVP K-30, Maize Starch, Purified Talc, Colloidal Anhydrous Silica (Aerosil), Magnesium Stearate, Insta Coat Universal (IC-U-1308) (White), Ponceau 4R.

6.2. Incompatibilities

None

6.3. Shelf life

36 Months.

6.4. Special precautions for storage

Store below 30^0C in a dry place. Protect from light.

Keep all medicines out of reach of children.

6.5. Nature and contents of container

1 X 10 Tablets packed in Alu-Alu Blister.

6.6. Instruction for use and handling

No special requirement

BRAND NAME:	**NARAFLOX**
GENERIC NAME:	**LEVOFLOXACIN TABLETS 500 MG**

7. Marketing Authorization Holder

MAXHEAL LABORATORIES PVT LTD

PLOT NO. - 2-7/80-85, SURSEZ,

G.I.D.C SACHIN, SURAT

GUJARAT-394230. INDIA

8. Marketing Authorization Number

Not Applicable.

9. Date of First Authorization /Renewal of the Authorization

Not Applicable.

10. Date of Revision of the

Not Applicable.