Pfiziflox tablets
(Levofloxacin)

1. NAME OF THE MEDICINAL PRODUCT

Pfiziflox

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains each film-coated tablet of 250 mg and 500 mg.

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

WARNING:
Fluoroquinolones, including Pfiziflox, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (see section **4.4 Special warnings and precautions for use**).

Pfiziflox is indicated in adults for the treatment of the following infections (see sections **4.4. Special warnings and precautions for use** and **5.1. Pharmacodynamic properties**):

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Pfiziflox (levofloxacin) and other antibacterial drugs, Pfiziflox should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Pfiziflox tablets are indicated for the treatment of adults (≥18 years of age) with mild, moderate, and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Culture and susceptibility testing

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to levofloxacin. Therapy with Pfiziflox may be initiated before results of these tests are known; once results become available, appropriate therapy should be selected.

As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with Pfiziflox Culture and susceptibility testing performed periodically

during therapy will provide information about the continued susceptibility of the pathogens to the antimicrobial agent and also the possible emergence of bacterial resistance.

Acute Bacterial Sinusitis: 5-day and 10-14 day Treatment Regimens

Pfiziflox is indicated for the treatment of acute bacterial sinusitis due to *Streptococcus pneumoniae, Haemophilus influenzae*, or *Moraxella catarrhalis.*

Acute Bacterial Exacerbation of Chronic Bronchitis

Pfiziflox is indicated for the treatment of acute bacterial exacerbation of chronic bronchitis due to methicillin-susceptible *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae*, or *Moraxella catarrhalis.*

Community-Acquired Pneumonia: 7-14 day Treatment Regimen

Pfiziflox is indicated for the treatment of community-acquired pneumonia due to methicillin-susceptible *Staphylococcus aureus, Streptococcus pneumoniae* (including multi-drug-resistant *Streptococcus pneumoniae* [MDRSP]), *Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydophila pneumoniae, Legionella pneumophila,* or *Mycoplasma pneumoniae.*

MDRSP isolates are strains resistant to two or more of the following antibiotics: penicillin (MIC ≥2 µg/ml), 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

Community-Acquired Pneumonia: 5-day Treatment Regimen

Pfiziflox is indicated for the treatment of community-acquired pneumonia due to *Streptococcus pneumoniae* (excluding multi-drug-resistant strains [MDRSP]), *Haemophilus influenzae, Haemophilus parainfluenzae, Mycoplasma pneumoniae, or Chlamydophila pneumoniae.*

Complicated Skin and Skin Structure Infections

Pfiziflox is indicated for the treatment of complicated skin and skin structure infections due to methicillin-susceptible *Staphylococcus aureus, Enterococcus faecalis, Streptococcus pyogenes,* or *Proteus mirabilis.*

In complicated skin and skin structure infections, Pfiziflox should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.

Uncomplicated Skin and Skin Structure Infections

Pfiziflox is indicated for the treatment of uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections, due to methicillin-susceptible *Staphylococcus aureus*, or *Streptococcus pyogenes.*

Chronic Bacterial Prostatitis

Pfiziflox is indicated for the treatment of chronic bacterial prostatitis due to *Escherichia coli, Enterococcus faecalis*, or methicillin-susceptible *Staphylococcus epidermidis*.

Acute Pyelonephritis and Complicated Urinary Tract Infections: 5-day Treatment Regimen

Pfiziflox is indicated for the treatment of complicated urinary tract infections due to *Escherichia coli, Klebsiella pneumoniae,* or *Proteus mirabilis.*

Acute Pyelonephritis and Complicated Urinary Tract Infections: 10-day Treatment Regimen

Pfiziflox is indicated for the treatment of complicated urinary tract infections (mild to moderate) due to *Enterococcus faecalis*, *Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* or *Pseudomonas aeruginosa*.

Acute Pyelonephritis: 5 or 10-day Treatment Regimen

Pfiziflox is indicated for the treatment of acute pyelonephritis caused by *Escherichia coli* including cases with concurrent bacteremia.

Uncomplicated Urinary Tract Infections

Pfiziflox is indicated for the treatment of uncomplicated urinary tract infections (mild to moderate) due to *Escherichia coli*, *Klebsiella pneumoniae*, or *Staphylococcus saprophyticus.*

Inhalational Anthrax (Post-Exposure)

Pfiziflox is indicated for inhalational anthrax (post-exposure) to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.* The effectiveness of Pfiziflox is based on plasma concentrations achieved in humans, a surrogate endpoint reasonably likely to predict clinical benefit. Pfiziflox has not been tested in humans for the post-exposure prevention of inhalation anthrax. The safety of Pfiziflox in adults for durations of therapy beyond 28 days or in pediatric patients for durations of therapy beyond 14 days has not been studied. Prolonged Pfiziflox therapy should only be used when the benefit outweighs the risk.

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

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Pfiziflox 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.

Duration of treatment: The duration of treatment varies according to the course of the disease (see table below). As with antibiotic therapy in general, administration of Pfiziflox tablets should be continued for

a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

Method of administration: Pfiziflox tablets should be swallowed without crushing and with sufficient amount of liquid. They may be divided at the score line to adapt the dosage. The tablets may be taken during meals or between meals. Pfiziflox tablets should be taken at least two hours before or after iron salts, antacids and sucralfate administration since reduction of absorption can occur.

Posology:
The following dose recommendations can be given for Pfiziflox:

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

Indication	**Daily dose regimen (according to severity)**	**Duration of treatment**
Acute bacterial sinusitis	500 mg once daily	10 - 14 days
Acute exacerbations of chronic bronchitis	250 to 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 urinary tract infections	250 mg once daily	3 days
Complicated urinary tract infections including pyelonephritis	250 mg once daily	7 - 10 days
Chronic bacterial prostatitis	500 mg once daily	28 days
Complicated skin and soft tissue infections	250 mg once daily or 500 mg 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 CAPD)[1]	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 Pfiziflox is not metabolised to any relevant extent by the liver and is mainly excreted by the kidneys.

In the elderly

No adjustment of dosage is required in the elderly, other than that imposed by consideration of renal function.

In children

Pfiziflox is contraindicated in children and growing adolescents (see section **4.3. Contraindications**).

Method of administration

Pfiziflox tablets should be swallowed without crushing and with sufficient amount of liquid. They may be divided at the score line to adapt the dose. The tablets may be taken during meals or between meals. Pfiziflox tablets should be taken at least two hours before or after iron salts, zinc salts, magnesium- or aluminium-containing antacids, or didanosine (*only didanosine formulations with aluminium or magnesium containing buffering agents*), and sucralfate administration, since reduction of absorption can occur (see section **4.5. Interaction with other medicinal products and other forms of interaction**).

4.3. CONTRAINDICATIONS

Levofloxacin must not be used:

• in patients hypersensitive to levofloxacin or other quinolones or any of the excipients,

• 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 Levofloxacin 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. Undesirable effects**). Treatment of these patients with Levofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section **4.3. Contraindications**).

In the most severe cases of pneumococcal pneumonia ,Levofloxacin may not be the optimal therapy.

Methicillin-resistant *S. aureus* are very likely to possess co-resistance to fluoroquinolones, 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).

Levofloxacin may be used in the treatment of Acute Bacterial Sinusitis and Acute Exacerbation of Chronic Obstructive Pulmonary Disease including 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 human 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.

Tendinitis and tendon rupture

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.

At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with Levofloxacin 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 levofloxacin tablets (including several weeks after treatment), may be symptomatic of *Clostridium difficile*-associated disease (CDAD), CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis (see section **4.8. Undesirable effects**). It is therefore important to consider this diagnosis in patients who develop serious diarrhoea during or after treatment with levofloxacin. If CDAD is suspected, levofloxacin tablets must be stopped immediately and patients should be treated with supportive measures ± 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. Levofloxacin is contraindicated in patients with a history of epilepsy (see section **4.3. Contraindications**) and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures or concomitant treatment with active substances that lower the cerebral seizure threshold, such as theophylline (see section **4.5. Interaction with other medicinal products and other forms of interaction**). In case of convulsive seizures (see section **4.8. Undesirable effects**), treatment with levofloxacin should be discontinued.

Patients with G-6-phosphate dehydrogenase deficiency

Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents. 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 levofloxacin should be adjusted in patients with renal impairment (see section **4.2. Posology and method of administration**).

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. Undesirable effects**). 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. Undesirable effects**). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Blood glucose disturbances (dysglycaemia)

As with other fluoroquinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with levofloxacin, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs in a patient being treated with levofloxacin it should be discontinued and appropriate therapy should be initiated immediately (see section **4.8. Undesirable effects**).

Development of drug resistant bacteria

Prescribing levofloxacin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Photosensitivity/Phototoxicity

Photosensitisation has been reported with levofloxacin (see section **4.8. Undesirable effects**). Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with the use of fluoroquinolones after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if photosensitivity/phototoxicity occurs.

Patients treated with Vitamin K antagonists

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

Central nervous system effects

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. Undesirable effects**). 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.

QT interval prolongation

Caution should be taken when using fluoroquinolones, including levofloxacin, have been associated with prolongation of the QT interval. Levofloxacin should be avoided in patients with known prolongation of the QT interval, patients with:

- Congenital long QT syndrome
- Concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA (quinidine, procainamide) and III (amiodarone, sotalol) antiarrhythmics, tricyclic antidepressants, macrolides).
- 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. (See sections **4.2 Posology and method of administration**-*Elderly*, **4.5. Interaction with other medicinal products and other forms of interaction**, **4.8. Undesirable effects**, and **4.9. Overdose**).
- Cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

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 Levofloxacin 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. Undesirable effects**)

Musculoskeletal disorders in pediatric patients

Levofloxacin is indicated in pediatric patients (≥6 months of age) only for the prevention of inhalational anthrax (post-exposure) (see section **4.1 Therapeutic indications**). An increased incidence of musculoskeletal disorders (arthralgia, arthritis, tendonopathy, and gait abnormality) compared to controls has been observed in pediatric patients receiving levofloxacin.

Hepatotoxicity

Post-marketing reports of severe hepatotoxicity (including acute hepatitis and fatal events) have been received for patients treated with levofloxacin. No evidence of serious drug-associated hepatotoxicity was detected in clinical trials of over 7,000 patients. Severe hepatotoxicity generally occurred within 14 days of initiation of therapy and most cases occurred within 6 days. Most cases of severe hepatotoxicity were not associated with hypersensitivity. The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not associated with hypersensitivity. Levofloxacin should be discontinued immediately if the patient develops signs and symptoms of hepatitis.

Exacerbation of myasthenia gravis

Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Post-marketing 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. Effects on ability to drive and use machines** and **4.8. Undesirable effects**).

Superinfection

The use of levofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms. If superinfection 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.

Other serious and sometimes fatal reactions

Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with fluoroquinolones, including levofloxacin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following:

- fever, rash, or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome);
- vasculitis; arthralgia; myalgia; serum sickness;
- allergic pneumonitis;
- interstitial nephritis; acute renal insufficiency or failure;
- hepatitis; jaundice; acute hepatic necrosis or failure;

- anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

The drug should be discontinued immediately at the first appearance of skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted.

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 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.

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

Antacids, Sucralfate, Metal Cations, Multivitamins

While the chelation by divalent cations is less marked than with other quinolones, concurrent administration of Levofloxacin with antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc may interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. Tablets with antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamins preparations with zinc or didanosine may substantially interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. These agents should be taken at least two hours before or two hours after levofloxacin administration.

Sucralfate

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

Theophylline

No significant effect of levofloxacin on the plasma concentrations, AUC, and other disposition parameters for theophylline was detected in a clinical study involving 14 healthy volunteers. Similarly, no apparent effect of theophylline on levofloxacin absorption and disposition was observed. However, concomitant administration of other quinolones with theophylline has resulted in prolonged elimination half-life, elevated serum theophylline levels, and a subsequent increase in the risk of theophylline-related adverse reactions in the patient population. Therefore, theophylline levels should be closely monitored and appropriate dosage adjustments made when levofloxacin is co-administered. Adverse reactions, including seizures, may occur with or without an elevation in serum theophylline levels.

Warfarin

No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for R- and S-warfarin was detected in a clinical study involving healthy volunteers. Similarly, no apparent effect of warfarin on levofloxacin absorption and disposition was observed. There have been reports during the post-marketing experience in patients that levofloxacin enhances the effects of warfarin. Elevations of the prothrombin time in the setting of concurrent warfarin and levofloxacin use have been associated with episodes of bleeding. Prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if levofloxacin is administered concomitantly with warfarin. Patients should also be monitored for evidence of bleeding.

Cyclosporine

No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for cyclosporine was detected in a clinical study involving healthy volunteers. However, elevated serum levels of cyclosporine have been reported in the patient population when co-administered with some other quinolones. Levofloxacin C_{max} and k_e were slightly lower while T_{max} and $t_{½}$ were slightly longer in the presence of cyclosporine than those observed in other studies without concomitant medication. The differences, however, are not considered to be clinically significant. Therefore, no dosage adjustment is required for levofloxacin or cyclosporine when administered concomitantly.

Digoxin

No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for digoxin was detected in a clinical study involving healthy volunteers. Levofloxacin absorption and disposition kinetics were similar in the presence or absence of digoxin. Therefore, no dosage adjustment for levofloxacin or digoxin is required when administered concomitantly.

Probenecid and Cimetidine

No significant effect of probenecid or cimetidine on the rate and extent of levofloxacin absorption were observed in a clinical study involving healthy volunteers. The AUC and $t_{½}$ of levofloxacin were 27–38% and 30% higher, respectively, while CL/F and CL_R were 21-35% lower during concomitant treatment with probenecid or cimetidine compared to levofloxacin alone. Although these differences were statistically significant, the changes were not high enough to warrant dosage adjustment for levofloxacin when probenecid or cimetidine is co-administered.

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

Non-steroidal anti-inflammatory drugs

The concomitant administration of a non-steroidal anti-inflammatory drug with a quinolone, including levofloxacin, may increase the risk of CNS stimulation and convulsive seizures.

Antidiabetic agents

Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with quinolones and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered.

Interactions with Laboratory or Diagnostic Testing

Some quinolones, including levofloxacin, may produce false-positive urine screening results for opiates using commercially available immunoassay kits. Confirmation of positive opiate screens by more specific methods may be necessary.

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. Special warnings and precautions for use**).

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. Special warnings and precautions for use** 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.

Food

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

4.6. FERTILITY, PREGNANCY AND LACTATION

Fertility

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

Use in pregnancy

Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day which correspond to 9.4 times the highest recommended human dose based upon relative body surface area or at intravenous doses as high as 160 mg/kg/day corresponding to 1.9 times the highest recommended human dose based upon relative body surface area. The oral dose of 810 mg/kg/day to rats caused decreased fetal body weight and increased fetal mortality. No teratogenicity was observed when rabbits were dosed orally as high as 50 mg/kg/day which correspond to 1.1 times the highest recommended human dose based upon relative body surface area, or when dosed intravenously as high as 25 mg/kg/day, corresponding to 0.5 times the highest recommended human dose based upon relative body surface area.

There are, however, no adequate and well-controlled studies in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section **5.3. Preclinical safety data**), levofloxacin must not be used in pregnant women (see sections **4.3.Contraindications** and **5.3. Preclinical safety data**).

Use in lactation

Levofloxacin has not been measured in human milk. Based upon data from ofloxacin, it can be presumed that levofloxacin will be excreted in human milk. In the absence of human data and due to that experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be used in breast-feeding women (see sections **4.3. Contraindications** and **5.3. Preclinical safety data**).

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Some 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 5000 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).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations	
Uncommon:	Fungal infection (and proliferation of other resistant microorganisms)
Blood and lymphatic system disorders	
Uncommon:	Leukopenia, eosinophilia
Rare:	Thrombocytopenia, neutropenia
Very rare:	Agranulocytosis
Not known:	Pancytopenia, haemolytic anaemia
Immune system disorders	
Very rare:	Anaphylactic shock Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose
Rare:	Hypersensitivity
Metabolism and nutrition disorders	
Uncommon:	Anorexia
Rare:	Hypoglycemia, particularly in diabetic patients
Psychiatric disorders*	
Uncommon:	Insomnia, nervousness
Rare:	Psychotic disorder, depression, confusional state, agitation, anxiety, abnormal dreams, nightmares
Very rare:	Psychotic reactions with self-endangering behaviour including suicidal ideation or acts, hallucination

Nervous system disorders*	
Common:	Headache, dizziness
Uncommon:	Somnolence, tremor
Rare:	Convulsion, paraesthesia
Very rare:	Sensory or sensorimotor peripheral neuropathy, dysgeusia including ageusia, parosmia including anosmia, extrapyramidal disorder, syncope, benign intracranial hypertension
Eye disorders*	
Rare:	Visual disturbance
Not known:	Transient vision loss
Ear and labyrinth disorders*	
Uncommon:	Vertigo
Very rare:	Hearing impaired
Not known:	Tinnitus
Cardiac disorders	
Rare:	Tachycardia, palpitation
Not known:	Ventricular tachycardia, which may result in cardiac arrest, electrocardiogram QT prolonged
Vascular disorders	
Rare:	Hypotension
Respiratory, thoracic and mediastinal disorders	
Rare:	Bronchospasm, dyspnoea
Very rare:	Pneumonitis allergic
Gastrointestinal disorders	
Common:	Diarrhoea, nausea, vomiting
Uncommon:	Abdominal pain, dyspepsia, flatulence, constipation
Rare:	Diarrhoea–haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis, pancreatitis
Hepatobiliary disorders	
Common:	Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)
Uncommon:	Blood bilirubin increased
Very rare:	Hepatitis
Not known:	Jaundice and severe liver injuries, including cases with acute liver failure, have been reported with levofloxacin, primarily in patients with severe underlying diseases.
Skin and subcutaneous tissue disorders	
Uncommon:	Rash, pruritus, hyperhidrosis
Rare:	Urticaria
Very rare:	Angioneurotic oedema, photosensitivity reaction
Not known:	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, hyperhidrosis Mucocutaneous reactions may sometimes occur even after the first dose, leukocytoclastic vasculitis, stomatitis
Musculoskeletal and connective tissue disorders*	
Rare:	Tendon disorder including tendinitis (e.g. Achilles tendon), arthralgia, myalgia,

	muscular weakness which may be of importance in patients with myasthenia gravis
Very rare:	Tendon ruptures. This undesirable effect may occur within 48 hours of starting treatment and may be bilateral, muscular weakness which may be of special importance in patients with myasthenia gravis
Not known:	Rhabdomyolysis
Renal and urinary disorders	
Uncommon:	Blood creatinine increased
Very rare:	Renal failure acute (e.g. due to nephritis interstitial)
General disorders and administration site conditions*	
Uncommon:	Asthenia
Very rare:	Pyrexia
Not known:	Pain (including pain in back, chest, and extremities)

*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. Special Precautions and Warnings for Use**).

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

- extrapyramidal symptoms and other disorders of muscular coordination,
- hypersensitivity vasculitis,
- attacks of porphyria in patients with porphyria

4.9. OVERDOSE

In the event of an acute overdosage, the stomach should be emptied. The patient should be observed and appropriate hydration maintained. Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

Levofloxacin exhibits a low potential for acute toxicity. Mice, rats, dogs and monkeys exhibited the following clinical signs after receiving a single high dose of Levofloxacin: ataxia, ptosis, decreased locomotor activity, dyspnea, prostration, tremors, and convulsions. Doses in excess of 1500 mg/kg orally and 250 mg/kg IV produced significant mortality in rodents

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: quinolone antibacterials, fluoroquinolones
ATC code: J01MA12

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

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 (C_{max}) 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]	≤1 mg/l	>1 mg/l
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 MIC's 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

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***
Bacillus anthracis *Staphylococcus aureus* methicillin-susceptible *Staphylococcus saprophyticus* *Streptococci,* group C and G *Streptococcus agalactiae* *Streptococcus pneumoniae* *Streptococcus pyogenes*
Aerobic Gram-negative bacteria *Eikenella corrodens* *Haemophilus influenzae* *Haemophilus para-influenzae* *Klebsiella oxytoca* *Moraxella catarrhalis* *Pasteurella multocida* *Proteus vulgaris* *Providencia rettgeri* ***Anaerobic bacteria*** *Peptostreptococcus* ***Other*** *Chlamydophila pneumoniae* *Chlamydophila psittaci* *Chlamydia trachomatis* *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[#] Coagulase negative *Staphylococcus* spp. ***Aerobic Gram-negative bacteria*** *Acinetobacter baumannii* *Citrobacter freundii* *Enterobacter aerogenes* *Enterobacter cloacae* *Escherichia coli* *Klebsiella pneumoniae* *Morganella morganii* *Proteus mirabilis* *Providencia stuartii* *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, including levofloxacin.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1 - 2 h. The absolute bioavailability is 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 bronchial mucosa, epithelial lining fluid, alveolar macrophages, lung tissue, skin (blister fluid), prostatic tissue and urine. However, levofloxacin has poor penetration into 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 and are 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 ($t_{½}$: 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 to 1000 mg.

Special populations

Subjects with renal insufficiency

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 500 mg 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 pharmacokinetics 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.

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. SHELF LIFE

24 Months

6.2. SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.3. HOW SUPPLIED

Pfiziflox is available as 250 mg and 500 mg tablets in the pack of 10's.

Pfiziflox/LPD/PK-04
According to Sanofi SPC Dated 17 July 2013

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Pfizer Pakistan Limited
B-2, S.I.T.E., Karachi-Pakistan.

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