Floxin-L®

Levofloxacin Hemihydrate

1.NAME OF THE MEDICINAL PRODUCT

Floxin-L® 250: Film coated tablets; Box of 7.

Floxin-L® 500: Film coated tablets; Box of 7.

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

Floxin-L® 250: Each film coated tablet contains levofloxacin hemihydrate equivalent to levofloxacin 250 mg.

Floxin-L® 500: Each film coated tablet contains levofloxacin hemihydrate equivalent to levofloxacin 500 mg.

For the full list of excipients, see section 6.1.

3.PHARMACEUTICAL FORM

Film-coated tablet.

4.CLINICAL PARTICULARS

4.1 Therapeutic indications

Floxin-L® is indicated in adults for the treatment of the following infections:

•Acute bacterial sinusitis

•Acute exacerbations of chronic bronchitis

•Community-acquired pneumonia

•Complicated skin and soft tissue infections

For the above-mentioned infections Floxin-L® should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.

•Pyelonephritis and complicated urinary tract infections

•Chronic bacterial prostatitis

•Uncomplicated cystitis

•Inhalation Anthrax: post exposure prophylaxis and curative treatment

Floxin-L® 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.

4.2 Posology and method of administration

Floxin-L® tablets are administered once or twice daily. The dosage depends on the type and severity of the infection and the susceptibility of the presumed causative pathogen.

Posology

The following dose recommendations can be given for Floxin-L® :

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

Indication	Daily dose regimen (according to severity)	Duration of treatment
Acute sinusitis	500 mg once daily	10 - 14 days
Acute 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
Complicated urinary tract infections	500 mg once daily	7 - 14 days
Uncomplicated Cystitis	250 mg once daily	3 days
Chronic bacterial Prostatitis	500 mg once daily	28 days
Complicated Skin and soft tissue infection	500 mg once or twice daily	7-14 daily
Inhalation Anthrax	500 mg once daily	8 weeks

Special populations

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

Creatinine clearance	Dosage regimen 250 mg/24 h	Dosage regimen 500 mg/24 h	Dosage regimen 500 mg/12 h
	First dose: 250 mg	First dose: 500 mg	First dose: 500 mg
50-20 ml/min	Then: 125 mg/24h	Then: 250 mg/24h	Then: 250 mg/12h
19-10 ml/min	Then: 125 mg/48h	Then: 125 mg/24h	Then: 125 mg/12h
< 10 ml/min (including hemodialysis and CAPD)[1]	Then: 125 mg/48h	Then: 125 mg/24h	Then: 125 mg/24h

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

Impaired liver function

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

Elderly Population

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

Pediatric population

Floxin-L® is contraindicated in children and growing adolescents.

Method of administration

Floxin-L® tablets should be swallowed without crushing and with sufficient amount of liquid. The tablets may be taken during meals or between meals. Floxin-L® tablets should be taken at least two hours before or after iron salts, zinc salts, magnesium- or aluminum-containing antacids, or didanosine (only didanosine formulations with aluminum or magnesium containing buffering agents), and sucralfate administration, since reduction of absorption can occur.

4.3 Contraindications

Levofloxacin tablets must not be used:

•In patients hypersensitive to levofloxacin or other quinolones or 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

-Methicillin resistant Staphylococcus aureus (MRSA) 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 Bronchitis when these infections have been adequately diagnosed.

-Resistance to fluoroquinolones of E. coli – the most common pathogen involved in urinary tract infections. 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 may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. Tendinitis and tendon rupture, sometimes bilateral, may occur within 48 hours of starting treatment with levofloxacin and have been reported up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in patients aged over 60 years, in patients receiving daily doses of 1000 mg and in patients using corticosteroids. The daily dose should be adjusted in elderly patients based on creatinine clearance. Close monitoring of these patients is therefore necessary if they are prescribed levofloxacin. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with levofloxacin must be halted immediately, and appropriate treatment (e.g. immobilization) must be initiated for the affected tendon.

-Clostridium difficile-associated disease (CDAD): Diarrhea, particularly if severe, persistent and/or bloody, during or after treatment with levofloxacin (including several weeks after treatment), may be symptomatic of CDAD. CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis. It is therefore important to consider this diagnosis in patients who develop serious diarrhea during or after treatment with levofloxacin. If CDAD is suspected or confirmed, levofloxacin should be stopped immediately and appropriate treatment initiated without delay. Anti-peristaltic medicinal products 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 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. 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-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 Floxin-L® should be adjusted in patients with renal impairment.

-Hypersensitivity reactions: Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema up to anaphylactic shock), occasionally following the initial dose. 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. Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

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

-Prevention of photosensitization: Photosensitization has been reported 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 photosensitization.

-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.

-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 behavior sometimes after only a single dose of levofloxacin. 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.

-Peripheral neuropathy: Peripheral sensory neuropathy and peripheral sensory motor neuropathy have been reported in patients receiving fluoroquinolones, including levofloxacin, which can be rapid in its onset. Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.

-Hepatobiliary disorders: Cases of hepatic necrosis up to fatal hepatic failure have been reported with levofloxacin, primarily in patients with severe underlying diseases, e.g. sepsis. 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

-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.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on Floxin-L®

-Iron salts, zinc salts, magnesium- or aluminum-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 Floxin-L® 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 Floxin-L® tablet administration. Calcium salts have a minimal effect on the oral absorption of levofloxacin.

-*Sucralfate:* The bioavailability of Floxin-L® tablets is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and Floxin-L®, it is best to administer sucralfate 2 hours after the Floxin-L® tablet administration.

-*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 affect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

Other relevant information:

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 Floxin-L® on other medicinal products

-*Ciclosporin:* The half-life of ciclosporin 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.

-*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).

Other forms of interactions

-*Food:* There is no clinically relevant interaction with food. Floxin-L® 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. However 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 pregnant women.

Breast-feeding

Floxin-L® 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 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.

Fertility

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

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

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:* Fungal, infection including Candida, infection, Pathogen resistance (uncommon).

-*Blood and lymphatic system disorders:* Leukopenia, Eosinophilia (uncommon); Thrombocytopenia, Neutropenia (rare); Pancytopenia, Agranulocytosis, Haemolytic anaemia (not known).

-*Immune system disorders:* Angioedema, Hypersensitivity (Rare); Anaphylactic shock, Anaphylactoid shock (not known).

-*Metabolism and nutrition disorders:* Anorexia (uncommon), Hypoglycaemia particularly in diabetic patients (rare); Hyperglycaemia, Hypoglycaemic coma (not known).

-*Psychiatric disorders:* Insomnia (common); Anxiety, Confusional state Nervousness (uncommon); Psychotic reactions (with e.g. hallucination, paranoia), Depression, Agitation, Abnormal dreams, Nightmares (rare); Psychotic disorders with self-endangering behavior including suicidal ideation or suicide attempt (not known).

-*Nervous system disorders:* Headache, Dizziness (common); Somnolence, Tremor, Dysgeusia (uncommon); Convulsion, Paraesthesia (rare); Peripheral sensory neuropathy, Peripheral sensory motor neuropathy, Parosmia including anosmia, Dyskinesia, Extrapyramidal disorder, Ageusia, Syncope, Benign intracranial hypertension (not known).

-*Eye disorders:* Visual disturbances such as blurred vision (rare); Transient vision loss, uveitis (not known).

-*Ear and Labyrinth disorders:* Vertigo (uncommon); Tinnitus (rare); Hearing loss, Hearing impaired (not known).

-*Cardiac disorders:* Tachycardia, Palpitation (rare); 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 (not known).

-*Vascular Disorders:* Hypotension (rare).

-*Respiratory, thoracic and mediastinal disorders*: Dyspnoea (uncommon); Bronchospasm, Pneumonitis allergic (not known).

-*Gastrointestinal Disorders:* Diarrhoea, Vomiting, Nausea (common); Abdominal pain, Dyspepsia, Flatulence, Constipation (uncommon); Diarrhoea – haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis, Pancreatitis (not known).

-*Hepatobiliary disorders:* Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT) (common); Blood bilirubin increased (uncommon); Jaundice and severe liver injury, including cases with fatal acute liver failure, primarily in patients with severe underlying diseases, Hepatitis (not known).

-*Skin and subcutaneous tissue disorders:* Rash, Pruritus Urticaria Hyperhidrosis (uncommon); Toxic epidermal necrolysis, Stevens-Johnson syndrome, Erythema multiforme, Photosensitivity reaction, Leukocytoclastic vasculitis, Stomatitis (not known).

-*Musculoskeletal and connective tissue disorders:* Arthralgia, Myalgia (uncommon); Tendon disorder including tendinitis (e.g. Achilles tendon), Muscular weakness which may be of importance in patients with myasthenia gravis (rare); Rhabdomyolysis, Tendon rupture (e.g. Achilles tendon), Ligament rupture, Muscle rupture, Arthritis (not known).

-*Renal and urinary disorders:* Blood creatinine increased (uncommon); Renal failure acute (e.g. due to interstitial) (rare).

-*General disorders and administration site conditions:* Asthenia (uncommon); Pyrexia (rare); Pain (including pain in back, chest, and extremities) (not known).

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 overdose of levofloxacin 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.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.

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).

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

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 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 100l after single and repeated 500mg 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 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 and are excreted in urine. Levofloxacin is stereochemically stable and does not undergo c
chiral inversion.

Elimination

Following oral and intravenous administration, levofloxacin is eliminated relatively slowly from the plasma (t½: 6 - 8 hours). 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.

6.PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Floxin-L® 250: Microcrystalline cellulose, croscarmellose sodium, povidone, magnesium stearate, hydroxypropyl methylcellulose, polysorbate, titanium dioxide, polyethylene glycol, red iron oxide.

Floxin-L® 500: Hypromellose, Crospovidone, Microcrystalline Cellulose, Sodium Stearyl Fumarate, Polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, yellow iron oxide and red iron oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 30°C.

Keep in original pack in intact conditions.

Date of revision

February, 2019

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

Benta S.A.L.
Dbayeh - Lebanon