ABLEVOX I.V

(Levofloxacin)

For intravenous infusion

Rx only

COMPOSITION

Each 100ml contains:

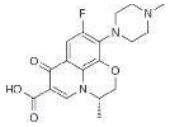
Levofloxacin Hemihydrate equivalent to

Levofloxacin 0.5g

Water for injection B.P.....Q.S

DESCRIPTION

Levofloxacin is a synthetic, broad-spectrum, third generation fluoroquinolone derivative antimicrobial agent for intravenous (I.V.) administration . Levofloxacin is (S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid. Its empirical formula is $C_{18}H_{20}FN_3O_4$ and its chemical structure is:



Levofloxacin is a light yellowish-white to yellow-white crystalline powder with a molecular weight of 361.368. Levofloxacin has the potential to form stable coordination compounds with many metal ions

CLINICAL PHARMACOLOGY

Levofloxacin mechanism of action involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination. Levofloxacin has cross resistance with other Fluoroquinolones, resistance can arise through mutations in defined regions of DNA gyrase or topoisomerase IV, termed the Quinolone-Resistance Determining Regions (QRDRs), or through altered efflux.

Fluoroquinolones, including levofloxacin, differ in chemical structure and mode of action from aminoglycosides, macrolides an d β-lactam antibiotics, including penicillins.

Fluoroquinolones may, therefore, be active against bacteria resistant to these antimicrobials.

Levofloxacin has in vitro activity against Gram-negative and Gram-positive bacteria and has been shown to be active against most isolates of the following bacteria both in vitro and in clinical infections,

Gram-Positive Bacteria; Enterococcus faecalis, Staphylococcus aureus (methicillin-susceptible isolates), Staphylococcus epidermidis (methicillin-susceptible isolates), Staphylococcus saprophyticus, Streptococcus pneumoniae (including multi-drug resistant isolates [MDRSP]), Streptococcus pyogenes

Gram-Negative Bacteria; Enterobacter cloacae, Escherichia coli, Haemophilus influenza, Haemophilus parainfluenzae, Klebsiella pneumonia, Legionella pneumophila, Moraxella catarrhalis, Proteus mirabilis, Pseudomon as aeruginosa, Serratiamarcescens

Other Bacteria; Chlamydophila pneumonia, Mycoplasma pneumoniae

Following Intravenous infusion, Levofloxacin is widely distributed into body tissues including the bronchial mucosa and lun gs, but penetration into cerebra spinal fluid is relatively poor. Levofloxacin is about 30 to 40% bound to plasma proteins. Only small amounts are metabolised, to inactive metabolites. The el imination half-life of levofloxacin is 6 to 8 hours, although this may be prolonged in patients with renal impairment. Levofloxacin is excreted largely unchanged, primarily in the urine with less than 5% as metabolites. It is not removed by haemodialysis or peritoneal dialysis

INDICATIONS AND USAGE

ABLEVOX I.V is indicated for the treatment of mild, moderate, and severe infections caused by susceptible isolates of the designated microorganisms.

Nosocomial Pneumonia; ABLEVOX I.V is indicated for the treatment of nosocomial pneumonia due to methicillin susceptible Staphylococcus aureus, Pseudomonas aeruginosa, Serratiamarcescens, Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae, or Streptococcus pneumoniae. Adjunctive therapy should be used as clinically indicated.

Where Pseudomonas aeruginosa is a documented or presumptive pathogen, combination therapy with an anti pseudomonal β-lactam is recommended.

Community-Acquired Pneumonia; ABLEVOX I.V is indicated for the treatment of community-acquired pneumonia due to methicillin-susceptible Staphylococcus aureus, Streptococcus pneumoniae (including multidrug-resistant Streptococcus pneumoniae[MDRSP]), Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydophila pneumoniae, Legionella pneumophila, or Mycoplasma pneumonia.

Complicated Skin and Skin Structure Infections; ABLEVOX I.V is indicated for the treatment of complicated skin and skin structure infections due to methicil lin-susceptible Staphylococcus aureus, Enterococcus faecalis, Streptococcus pyogenes , or Proteus mirabilis.

Uncomplicated Skin And Skin Structure Infections; ABLEVOX I.V is indicated for the treatment of uncomplicated skin and skin structure infections (mi ld to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections, due to methicillin-susceptible Staphylococcus aureus, or Streptococcus pyogenes.

Chronic Bacterial Prostatitis; ABLEVOX I.V is indicated for the treatment of chronic bacterial prostatitis due to Escherichia coli, Enterococcus faecalis, or methicillin-susceptible Staphylococcus epidermidis.

Inhalational Anthrax (Post-Exposure); ABLEVOX I.V is indicated for inhalational anthrax (post-exposure) to reduce the incidence or progression of disease following exposure to aerosolized Bacillus anthracis.

Plague; ABLEVOX I.V is indicated for treatment of plague, including pneumonic and septicemic plague, due to Yersinia pestis (Y. pestis) and prophylaxis for plague in adults and paediatric patients, 6 months of age and older.

Complicated Urinary Tract Infections; ABLEVOX I.V is indicated for the treatment of complicated urinary tract infections due to Escherichia coli, Klebsiella pneumoniae, or Proteus mirabilis.

Acute Pyelonephritis; ABLEVOX I.V is indicated for the treatment of acute pyelonephritis caused by Escherichia coli, including cases with concurrent bacteremia.

Uncomplicated Urinary Tract Infections; ABLEVOX I.V is indicated for the treatment of uncomplicated urinary tract infections (mild to moderate) due to Escherichia coli, Klebsiella pneumoniae, or Staphylococcus saprophyticus. Because fluoroquinolones, including ABLEVOX, have been associated with serious adverse reactions and for some patients uncomplicated urinary tract infection is self-limiting, reserve ABLEVOX for treatment of uncomplicated urinary tract infections in patients who have no alternative treatment options.

Acute Bacterial Exacerbation of Chronic Bronchitis; ABLEVOX I.V is indicated for the treatment of acute bacterial exacerbation of chronic bronchitis (ABECB) due to methicillin-susceptible Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus para influenzae, or Moraxella catarrhalis

Acute Bacterial Sinusitis; ABLEVOX I.V is indicated for the treatment of acute bacterial sinusitis (ABS) due to Streptococcus pneumoniae, Haemophilus influenzae, or Moraxella catarrhalis

DRUG INTERACTIONS

Effect of other medicinal products on ABLEVOX I.V.

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.

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. H owever, 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 co -administered 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 releva nt extent when levofloxacin was administered together with the following drugs: calcium carbonate, digoxin, glibenclamide, ranitidine.

Effect of ABLEVOX I.V 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 levofl oxacin in combination with a vitami K antagonist (e.g. warfarin). Coagulation tests, therefore, should be monitored in patients tr eated 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 in terval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

Other relevant information

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

ADVERSE REACTIONS

The information given below is based on data from clinical studies in more than 8 ,300 patients and on extensive post marketing experience.

Frequencies in this table are defined using the following convention:

Very common	(≥1/10),
Common	(≥1/100 to <1/10),
Uncommon	(≥1/1000 to <1/100),
Rare	(≥1/10000 to <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.

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 the lymphatic system disorders		Leukopenia Eosinophilia	Thrombocytopenia Neutropenia	Pancytopenia Agranulocytosis Haemolyticanaemia
Immune system disorders			Angiodema Hypersensitivity	Anaphylactic[a] shock and Anaphylactoid[a]shock
Metabolism and nutrition disorders		Anorexia	Hyperglycaemia particularly in diabetic patients	Hyperglycaemia Hypoglycaemic coma
Psychiatric disorders	Insomnia	Anxiety Confusional state Nervousness	Psychotic reactions (with eg hallucination, paranoia), Depression Agitation Abnormal dreams Nightmares	Psychotic with self-endangering behaviour including suicidal ideation or suicide attempt.
Nervous system disorders	Headache Dizziness	Somnolence Tremor Dysgeusia	Convulsion, Paraesthesia	Peripheral sensory neuropathy Peripheral sensory motor neuropathy Parosmia including anosmia Dyskinesia Extrapyramidal disorder Agnesia Syncope Benign intracranial hypertension
Eye disorders			Visual disturbances such as blurred vision,	Transient vision loss.
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.
Vascular disorders	PhIebitis		Hypotension	
Respiratory, thoracic and mediastinal disorders		Dyspnoea		Bronchospasm Pneumonitis allergic
Gastro-intestinal disorders	Diarrhoea Vomiting Nausea	Abdominal pain Dyspepsia Flatulence Constipation		Diarrhoea – haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis Pancreatitis
Hepatobiliary disorders	Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)	Blood bilirubin increased		Jaundice and severe liver injury, including fatal cases with acute liver failure, primarily in patients with severe underlying diseases Hepatitis
Skin and subcutaneous tissue disorders [b]		Rash Pruritus Urticaria Hyperhidrosis		Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Photosensitivity reaction Leukocytoclastic vasculitis Stomatitis

Usage

Due to severe side effects, to reduce the development of drug-resistant bacteria and maintain the effectiveness of ABLEVOX I.V and other fluoroquinolones, ABLEVOX should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and s usceptibility information are available, they should be considered in selecting or modifying antibacterial the rapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

ABLEVOX I.V is contraindicated in persons with history of hypersensitivity to Levofloxacin, any member of the quinolone class of antimicrobial agents, or any of the product components.

Paediatrics: Levofloxacin should be used in paediatric and young adult patients (less than 18 years of age) only for the infections listed in the INDICATIONS AND USAGE section.

PRECAUTIONS AND WARNINGS

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 a ntibacterial agents for the treatment of MRSA infections are considered inappropriate).

Resistance to fluoroquinolones of E. Coli – the most common pathogen involved in urinary tract infections – varies across regions. 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 sh ould refer to national and/or international consensus documents regarding the treatment of anthrax.

Infusion time: The recommended infusion time of at least 60 minutes for 500 mg levofloxacin should be observed. It is known for ofloxacin, that during infusion tachycardia and a temporary decrease in blood pressure may develop. In rare cases, as a consequence of a profound drop in bloo d pressure, circulatory collapse may occur. If a conspicuous drop in blood pressure occur during infusion of levofloxacin, (i-somer of ofloxacin) the infusion must be halted immediately.

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 afte r discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in patients aged over 60 years, in patients receiving daily doses of 1000mg 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 th eir physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with levofloxacin must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated f or the affected tendon.

Clostridium difficile-associated disease; Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with levoflox acin, (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 pseudom embranous colitis. It is therefore important to consider this diagnosis in patients who develop serious diarrhoea during or after treatment with levofloxacin. If CD AD 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 histo ry of epilepsy and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures, or concomitant treatment with acti ve substances which 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 monitor ed.

Patients with renal impairment; since levofloxacin is excreted mainly by the kidneys, the dose medicinal product should be adju sted in patients with renal impairment.

Hypersensitivity reactions; Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema up to anaphylactic shock), occa sionally following the initial dose. Patients should discontinue treatment immediately and contact their physician or an emergency physician, who will initiate appropriate emergency measur es.

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 ultraviolet (UV) rays (e.g. sunray lamp, solarium), during treatment and for 48 hours following treatment discontinuation, in or der 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 behaviour - 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.

QT interval prolongation; Caution should be taken when using fluoroquinolones, including levofloxacin, in patients with known risk factors for prolongation of the Q T interval.

Peripheral neuropathy; Peripheral sensory neuropathy and peripheral motor sensory neuropathy have been reported in patients receiving fluoroquinolon es, including levofloxacin, which can be rapid in its onset. Levofloxacin should be discontinued if the patient experiences symptom s 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 anorexi a, 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. 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 immedia tely.

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.

olone administration include:

• attacks of porphyria in patients with porphyria.

OVERDOSAGE

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 levofloxacin are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval. 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. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in rem oving levofloxacin from the body. No specific antidote exists.

DOSAGE AND ADMINISTRATION

ABLEVOX I.V. should be administered as follows:

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

Indication	Daily dose regimen (according to severity)	Total duration of treatment*(according to severity)
Community-acquired pneumonia	500 mg once or twice daily	7–14 days
Pyelonephritis	500mg once daily	7–10 days
Complicated urinary tract infections	500 mg [1] once daily	7–14 days
Chronic bacterial prostatitis	500 mg once daily	28 days
Complicated skin and soft tissue infections	500 mg once or twice daily	7–14 days
Inhalation anthrax	500 mg once daily	8 weeks

*Treatment duration includes intravenous plus oral treatment. The time to switch from intravenous to oral treatment depends on the clinical situation, but is normally 2 to 4 days.

Special populations:

Patients with renal impairment (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).

Patients with hepatic impairment

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.

Older people

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

Paediatric population

Refer to CONTRAINDICATIONS.

Method of administration

ABLEVOX I.V solution for infusion is only intended for slow intravenous infusion; it is administered once or twice daily. The infusion ti me must be at least 30 minutes for 250 mg or 60 minutes for 500 mg levofloxacin.

Parenteral drug products should be inspected vis ually for particulate matter and discoloration prior to administration .

Presentation

Clear, greenish yellow or faintly yellow solution in sterile plastic bottle of 100ml

Shelf life

The manufacturing and expiry dates are indicated on the packing.

Storage

Store below 30º C but do not freeze, protect from light.

Registration Number(s) : 9809/06/17

Date of first Authorization : 14th June 2017

Date of Revision : 04th January 2017

Next Date of Revision : 04th January 2020

Manufactured by:

Abacus Parenteral Drugs Ltd.

Factory: Block 191, Plot No. 114, Kanga, Mukono.

Head Office: P.O. Box. 31376 Kampala, Uganda.

Tel: +256 312 380800, Fax: +256 312 380800,

E-mail: apdl@kilokogroup.com,

website: www.abacusparenteral.com