SUMMARY OF PRODUCT CHARACTERISTICS

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

- Fluoroquinolones, including Levofloxacin, the active ingredient of FLOXILEVO have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together, including:
  - Tendinitis and tendon rupture
  - Peripheral neuropathy
  - Central nervous system effects

  Discontinue FLOXILEVO immediately and avoid the use of fluoroquinolones in patients who experience any of these serious adverse reactions

- Fluoroquinolones, including FLOXILEVO, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid FLOXILEVO in patients with a known history of myasthenia gravis.

- Because fluoroquinolones, including FLOXILEVO, have been associated with serious adverse reactions, reserve for use in patients who have no alternative treatment options for the following indications:
  - Acute bacterial sinusitis
  - Acute bacterial exacerbation of chronic bronchitis

1. NAME OF THE MEDICINAL PRODUCT

FLOXILEVO 750 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains
Active substance: 768.69 mg levofloxacin hemihydrate equivalent to 750 mg levofloxacin.

Excipient(s):
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.
White film coated odorless, homogenous oblong tablets, engraved DEVA on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It should not be used in acute bacterial sinusitis and acute bacterial exacerbation of chronic bronchitis in the presence of alternative treatment options due to the risk of serious side effects. In addition to this susceptibility has to be proven with antibiogram test in urinary tract infections.

FLOXILEVO is indicated in adults for the treatment of the following infections if caused by

levofloxacin-susceptible microorganisms:

- Acute sinusitis
  due to *Streptococcus pneumoniae, Haemophilus influenzae* or *Moraxella catarrhalis.*
- Acute exacerbation of chronic bronchitis
  due to *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae* or *Moraxella catarrhalis.*
- Community-acquired pneumonia
  due to *Staphylococcus aureus, Streptococcus pneumoniae* (including penicillin-resistant strains with MIC value ≥2 µg/ml for penicillin) *Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae, Legionella pneumophila* or *Mycoplasma pneumonia.*
- Complicated urinary tract infections including pyelonephritis
  acute pyelonephritis caused by *Escherichia coli,* complicated urinary tract infections due to *Enterococcus faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* or *Pseudomonas aeruginosa.*
- Prostatitis
  due to *Escherichia coli, Enterococcus faecalis* or *Stapylococcus epidermidis.*
- Skin and soft tissue infections
  complicated skin and skin structures infections due to methicillin-susceptible *Staphylococcus aureus, Enterococcus faecalis, Streptococcus pyogenes or Proteus mirabilis* and uncomplicated skin and skin structures infections including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections due to *Staphylococcus aureus* or *Streptococcus pyogenes.*
- Inhalational Anthrax
  For prophylaxis and curative treatment after exposure to aerosolized *Bacillus anthracis.*

For suitable use of anti-bacterial agents and local susceptibility of pathogens, official national guides should be taken into consideration (see section 4.4).

4.2 Posology and method of administration

FLOXILEVO is administered once or twice daily. The dosage depends on the type and severity of infection and also susceptibility of the causative pathogen.

Posology/administration frequency and duration:

FLOXILEVO is recommended to be used in adults at following doses:

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

Indication	**Daily dosage regimen** *(according to severity of infection)*	**Duration of treatment** *(according to severity of infection)*
Acute sinusitis**	500 mg once daily	10-14 days
Acute exacerbation of chronic bronchitis**	250 mg-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
Skin and skin structure infections	250 mg once daily or	7-14 days

	500 mg once or twice daily	
Chronic bacterial prostatitis	500 mg once daily	28 days
Inhalational Anthrax	500 mg once daily	8 weeks

** Consideration should be given to increasing the dose in cases of severe infection.*
*** For oral use only*

Method of administration:
FLOXILEVO should be swallowed without crushing and with sufficient amount of liquid. The film coated tablets may be taken during meals or between meals. FLOXILEVO tablets should be taken at least 2 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 (see section 4.5).

Duration of treatment
The duration of therapy varies according to the course of the disease (see table above). As with antibiotic therapy in general, administration of FLOXILEVO should be continued for a minimum of 48 to 72 hours after the patient has become afebrile and evidence of bacterial eradication has been obtained.

Additional information on special populations:
Renal insufficiency:
It is used as indicated on following table.

Dosage for patients with creatinine clearance ≤50 ml/minute (according to severity of infection)			
	250 mg/24 hours	**500 mg/24 hours**	**500 mg/12 hours**
Creatinine clearance	**first dose 250 mg**	**first dose 500 mg**	**first dose 500 mg**
50-20 ml/minute 19-10 ml/minute	then: 125 mg/24 hours then: 125 mg/48 hours	then: 250 mg/24 hours then: 125 mg/24 hours	then: 250 mg/12 hours then: 125 mg/12 hours
<10 ml/minute (together with hemodialysis and continuous ambulatory peritoneal dialysis)*	then: 125 mg/48 hours	then: 125 mg/24 hours	then: 125 mg/24 hours

** No additional doses are required after hemodialysis or continuous ambulatory peritoneal dialysis.*

Hepatic impairment:
Levofloxacin is metabolized to a very low extent in the liver and is eliminated primarily via the kidneys. Therefore, no dosage adjustment is required in hepatic insufficiency.

Pediatric population:
FLOXILEVO is contraindicated in children and growing adolescents (see section 4.3).

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

4.3 Contraindications

FLOXILEVO (levofloxacin) should not be used in following cases:
- In patients hypersensitive to levofloxacin, or other fluoroquinolone antibacterial medicine or any of the excipients of FLOXILEVO
- 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

It is contraindicated in children, growing adolescents, during pregnancy and in breastfeeding women because – based on animal studies – risk of damage to weight-bearing cartilage of the growing organism cannot be excluded.

4.4 Special warnings and precautions for use

Disabling and potentially irreversible serious adverse reactions including tendinitis and tendon rupture, peripheral neuropathy, and central nervous system effects
Fluoroquinolones, including FLOXILEVO, have been associated with disabling and potentially irreversible serious adverse reactions. Commonly seen adverse reactions include musculoskeletal and peripheral nervous system effects (such as tendonitis, tendon rupture, swelling or inflammation of tendons, tingling or numbness, numbness in arms and legs, muscle pain, muscle weakness, joint pain, joint swelling), arthralgia, myalgia, peripheral neuropathy and central nervous system effects (hallucination, anxiety, depression, suicidal ideation, insomnia, severe headache and confusion) (see section 4.8).

These reactions can occur within hours to weeks after starting FLOXILEVO. Patients of any age or without pre-existing risk factors have experienced these adverse reactions.

Discontinue FLOXILEVO immediately at the first signs or symptoms of any serious adverse reaction. In addition, avoid the use of fluoroquinolones, including FLOXILEVO, in patients who have experienced any of these serious adverse reactions associated with fluoroquinolones.

General warnings
The prevalence of acquired resistance may vary from country to country and with time for some types of bacteria. Therefore local information on resistance is desirable; particularly in severe infections or when response to treatment cannot be obtained, pathogen should be isolated and microbiological diagnosis should be made and evidence for susceptibility of the pathogen should be sought.
FLOXILEVO may not be the most appropriate treatment for very severe cases of pneumococcal pneumonia.

Nosocomial infections due to *P. aeruginosa* may require combination therapy.

Methicillin-resistant S. aureus:
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.

Patients predisposed to convulsions:

As with other quinolones, FLOXILEVO is contraindicated in patients with a history of epilepsy.

It should be used with extreme caution in patients predisposed to seizures, such as patients with pre-existing central nervous system damage; concomitant treatment with fenbufen and similar non-steroidal anti-inflammatory drugs or with drugs which lower the cerebral seizure threshold, such as theophylline (see section 4.5). In case of convulsive seizures, treatment with levofloxacin should be discontinued.

Clostridium difficile-associated disease (Pseudomembranous colitis):
Diarrhea, particularly if severe, persistent and/or bloody, during or after treatment with FLOXILEVO, may be symptomatic of *Clostridium difficile*-associated disease. This is the most serious form of pseudomembranous enterocolitis. If pseudomembranous enterocolitis is suspected, FLOXILEVO therapy should be discontinued immediately and appropriate supportive and/or specific therapy (e.g. oral vancomycin, teicoplanin or metronidazole) should be started without delay. In this clinical situation, drugs that inhibit intestinal motility are contraindicated.

Tendinitis and tendon rupture:
Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. This undesirable effect may occur within 48 hours of starting treatment and may be bilateral. The risk of tendon rupture is increased in the elderly, in patients receiving daily doses of 1000 mg and in patients using corticosteroids. Close monitoring of these patients is therefore necessary if they are prescribed FLOXILEVO. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with FLOXILEVO must be halted immediately, and appropriate treatment (e.g. immobilization) must be initiated for the affected tendon.

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

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

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

QT interval prolongation:
Prolongation of the QT interval has been reported in patients given fluoroquinolones, including levofloxacin, though very rarely.
Caution should be taken when using fluoroquinolones, including levofloxacin, in patients with known risk factors for prolongation of the QT interval such as:
- Uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)
- Congenital long QT syndrome

- Cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
- Concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics)

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.

Dysglycemia:
As with all quinolones, changes in blood glucose, including both hypoglycemia and hyperglycemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glibenclamide) or with insulin. Cases of hypoglycemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see section 4.8).

Exacerbation of Myasthenia Gravis:
Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in persons 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.

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

Development of sensitivity to light (Photosensitization):
Although photosensitization due to levofloxacin is very rare, patients are advised to avoid strong sunlight or artificial ultraviolet rays such as solariums during treatment and for 48 hours after stopping treatment.

Superinfection:
As with other antibiotics, prolonged use of levofloxacin may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs, appropriate measures should be taken.

Patients with glucose-6-phosphate dehydrogenase deficiency:
Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to hemolytic reactions when treated with quinolone antibacterial agents, therefore levofloxacin should be used with caution in such patients.

Peripheral neuropathy:
Sensory or sensory-motor peripheral 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.

Inhalation anthrax:
Use in humans is based on *in vitro Bacillus anthrasis* 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.

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

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

Visual disturbances:
If visual disturbances or any other eye effects occur, an examination by an ophthalmologist should be performed immediately (see sections 4.7 and 4.8).

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 methods.

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

Magnesium or aluminum or iron or zinc containing medicines, didanosine:
Since the absorption of levofloxacin is markedly reduced when it is administered with preparations containing divalent or trivalent cations, such as iron salts, or with drugs containing magnesium and aluminium (e.g. antacids), these drugs should be administered at least two hours before or 2 hours after the administration of FLOXILEVO (see section 4.2).

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

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

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

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

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 medicines 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.

Cyclosporine
The half-life of cyclosporine 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.

Patients should be carefully monitored in respect of indication of bleeding (see section 4.4).

Medicines known to prolong QT interval
Levofloxacin, like other fluoroquinolones, should be used with caution in patients receiving medicines known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4, prolongation of the QT interval).

Others
Clinical pharmacology studies have shown that there is no clinically significant change in the pharmacokinetics of levofloxacin when administered concomitantly with digoxin, glibenclamide, ranitidine, and calcium carbonate.

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, FLOXILEVO may therefore be administered regardless of food intake.

Additional information on special populations
There is no data for specific populations.

Pediatric population:
There is no data on pediatric population.

4.6 Fertility, pregnancy and lactation
General principles
Pregnancy category is C.

There is not sufficient data on the use of levofloxacin in pregnant women.

Women of child-bearing potential/Birth control (Contraception)

There is not sufficient data available on the use in women of child-bearing potential.

Pregnancy
Animal studies are insufficient with respect to effects on pregnancy and/or embryonal/fetal development and/or parturition and/or postnatal development (see sections 4.3 and 5.3). The potential risk for humans is unknown. However, in the absence of human data and due to the experimental data that suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, FLOXILEVO must not be used in pregnant women.

Breastfeeding
There is insufficient/limited information on the excretion of levofloxacin in human or animal milk.

A risk to the breast-fed child cannot be excluded due to the physicochemical and available pharmacodynamic/toxicological data on the excretion of levofloxacin in milk. FLOXILEVO should not be used during breast-feeding because of the risk of damage to weight-bearing cartilage in growing organisms demonstrated in experimental studies with fluoroquinolones (see sections 4.3 and 5.3).

Reproductive ability/Fertility
There is not sufficient data available on the effects of FLOXILEVO on fertility in humans.

4.7 Effects on ability to drive and use machines
The use of FLOXILEVO may cause some undesirable side effects such as dizziness/vertigo, visual disturbances, and drowsiness, which may impair the patient's ability to concentrate and react. In situations requiring special attention, such as driving and using machines, a decrease in these abilities may pose a risk. Patients who experience such side effects while using FLOXILEVO should not drive or use machines.

4.8 Undesirable effects
The information given below is based on data from clinical studies in more than 8300 patients and on extensive post marketing experience.
Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), 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 infections, pathogen resistance

Blood and lymphatic system disorders
Uncommon: Leucopoenia, eosinophilia
Rare: Neutropenia, thrombocytopenia
Not known (post-marketing data): Pancytopenia, agranulocytosis, hemolytic anemia

Immune system disorders
Rare: Angioedema, hypersensitivity
Not known (post-marketing data): Anaphylactic shock, anaphylactoid shock
Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose (see section 4.4).

Metabolism and nutrition disorders
Uncommon: Anorexia
Rare: Hypoglycemia, particularly in diabetic patients (see section 4.4)
Not known: Hyperglycemia, hypoglycemic coma (see section 4.4)

Psychiatric disorders
Common: Insomnia
Uncommon: Anxiety, confusional state, nervousness
Rare: Psychotic disorder (e.g. together with hallucinations, paranoia), depression, agitation, abnormal dreams, nightmares
Not known (post-marketing data): Psychotic disorders with self-endangering behavior including suicidal ideation or suicide attempt

Nervous system disorders
Common: Headache, dizziness
Uncommon: Somnolence, tremor, taste disturbance (dysgeusia)
Rare: Paresthesia, convulsions (see section 4.4),
Not known (post-marketing data): Sensory or sensory-motor peripheral neuropathy (see section 4.4), dyskinesia, extrapyramidal disorder, loss of taste (ageusia), loss of smell (anosmia), olfactory disorders (parosmia), syncope, benign intracranial hypertension

Eye disorders
Rare: Visual disturbances including blurred vision
Not known: Transient vision loss (see section 4.4)

Ear and labyrinth disorders
Uncommon: Vertigo
Rare: Tinnitus
Not known: Impaired hearing, hearing loss

Cardiac disorders
Rare: Tachycardia, palpitation
Not known (post-marketing data): Torsade de pointes, ventricular arrhythmia, ventricular tachycardia, prolongation of QT interval on electrocardiogram, which may result in cardiac arrest (see sections 4.4 and 4.9)

Vascular disorders
Rare: Hypotension

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnea
Not known (post-marketing data): Bronchspasm, pneumonitis allergic

Gastrointestinal disorders
Common: Diarrhea, vomiting, nausea
Uncommon: Abdominal pain, dyspepsia, flatulence, constipation
Not known (post-marketing data): Diarrhea – hemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis (see section 4.4), pancreatitis.

Hepatobiliary disorders
Common: Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)
Uncommon: Blood bilirubin increased
Not known (post-marketing data): Severe liver injury, jaundice
Cases of acute liver failure, sometimes fatal, have been reported with levofloxacin, primarily in patients with serious underlying disease (see section 4.4), hepatitis.

Skin and subcutaneous tissue disorders
Uncommon: Pruritus, redness, urticaria, hyperhidrosis
Not known: Toxic epidermal necrolysis, Stevens-Johnson syndrome (see section 4.4), erythema multiforme, photosensitivity reaction (see section 4.4), leukocytoclastic vasculitis, stomatitis
Mucocutaneous reactions may sometimes occur even after the first dose.

Musculoskeletal and connective tissue disorders
Uncommon: Arthralgia, myalgia
Rare: Tendon disorder including tendinitis (see section 4.4) (may occur, for example, in the achilles tendon), muscular weakness which may be of special importance in patients with myasthenia gravis (see section 4.4 exacerbation of Myasthenia Gravis)
Not known (post-marketing data): Rhabdomyolysis, tendon rupture (e.g. Achilles tendon) (see section 4.4), ligament rupture, muscle rupture, arthritis

Renal and urinary disorders
Uncommon: Blood creatinine increased
Rare: Renal failure acute (e.g. due to interstitial nephritis)

General disorders and administration site conditions
Uncommon: Asthenia
Rare: Pyrexia
Not known: Pain (in back, chest, and extremities)

Other undesirable effects which have been associated with fluoroquinolones administration:
Very rare: Attacks of porphyria in patients with porphyria

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Symptoms:
According to toxicity studies in animals, the most important signs to be expected following acute overdose of FLOXILEVO are confusion, dizziness, impairment of consciousness, and convulsive seizures. Central nervous system effects, including confusional state, convulsions, hallucinations, and tremor, have been observed in post-marketing experience. Gastrointestinal reactions include nausea and mucosal erosions.
In clinical pharmacology studies performed with supra-therapeutic doses, prolongation of QT interval has been observed.

Treatment:

In case of overdose, the patient should be monitored carefully, ECG monitoring should be performed and symptomatic treatment should be applied since there is a possibility of QT interval prolongation. Antacids may be used for protection of gastric mucosa.

Hemodialysis, peritoneal dialysis, or continuous ambulatory peritoneal dialysis 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. It is the S(-) enantiomer of the racemic drug substance ofloxacin.

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

Antibacterial spectrum
The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections.

Levofloxacin has been shown to be active against the following pathogens *in vitro*:

Gram-positive aerobes: *Bacillus anthracis, Corynebacterium diphtheriae, Enterococcus faecalis*, Enterecoccus* spp*, Listeria monocytogenes,* Coagulase negative staphylococci (methicillin susceptible), *Staphylococcus aureus* (methicillin susceptible)*, *Staphylococcus epidermidis* (methicillin susceptible), *Staphylococcus saprophyticus,* Group C and G streptococci*, Streptococcus agalactiae, Streptococcus pneumoniae* (penicillin susceptible/intermediately resistant/resistant)*, *Streptococcus pyogenes*,* Viridans streptococci *(penicillin resistant/susceptible)*

Gram-negative aerobes: *Acinetobacter baumannii, Acinetobacter* spp*, Actinobaccillus actinomycetemcomitans, Citrobacter freundii*, Eikenella corrodens, Enterobacter aerogenes, Enterobacter cloacae*, Enterobacter* spp, *Escherichia coli*, Gardnerella vaginalis, Haemophilus ducreyi, Haemophilus influenzae** (ampicillin susceptible/resistant), *Haemophilus parainfluenzae*, Helicobacter pylori, Klebsiella oxytoca, Klebsiella pneumoniae*, Klebsiella* spp*, Moraxella catarrhalis* (beta-lactamase-positive /beta-lactamase-negative)*, *Morganella morganii*, Neisseria gonorrhoeae* (penicillase producing/non-penicillase producing), *Neisseria meningitidis, Pasteurella canis, Pasteurella dagmatis, Pasteurella multocida, Pasteurella* spp, *Proteus mirabilis*, Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Providencia* spp*, Pseudomonas aeruginosa**, Pseudomonas* spp, *Salmonella* spp, *Serratia marcescens*, Serratia* spp.

Anaerobes: *Bacteroides fragilis, Bifidobacterium* spp*, Clostridium perfringens, Fusobacterium* spp*, Peptostreptococcus, Propionibacterium* spp, *Veillonella* spp

Others: Bartonella spp, *Chlamydia pneumoniae*, Chlamydia psittaci, Chlamydia trachomatis, Legionella pneumophila*, Legionella* spp, *Mycobacterium* spp*, Mycobacterium leprae,*

Mycobacterium tuberculosis,, Mycoplasma hominis, Mycoplasma pneumoniae Rickettsia* spp*, Ureaplasma urealyticum.*

Intermediately susceptible microorganisms:
Gram-positive aerobes: *Corynebacterium urealyticum, Corynebacterium xerosis, Enterococcus faecium, Staphylococcus epidermidis (*methicillin resistant*), Staphylococcus haemolyticus* (methicillin resistant).

Gram-negatif aerobes: *Campylobacter jejuni/coli*

Anaerobes: *Clostridium difficile, Prevotella* spp *and Porphyromonas* spp

Resistant microorganisms:
Gram-positive aerobes: *Corynebacterium jeikeium, Staphylococcus* coagulase negative methi-R, *Staphylococcus aureus* (methicillin resistant)

Gram-negative aerobes: *Alcaligenes xylosoxidans*

Anaerobes: *Bacteriodes thetaiotaomicron*

Others: *Mycobacterium avium*
* Clinical efficacy has been proven in clinical studies.
*** Combination therapy may be required in nosocomial infections caused by Pseudomonas aeruginosa.*

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

Breakpoints
The European Committee on Antimicrobial Susceptibility Testing (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 MICs of 0.12-0.5 mg/l) may occur but there is no evidence that this resistance is of clinical importance in respiratory tract infections with *H. influenzae*.
[3] Strains with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate must be sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant.
[4] Breakpoints apply to an oral dose of 500 mg x 1 to 500 mg x 2 and an intravenous dose of 500 mg × 1 to 500 mg × 2.

The prevalence of resistance may vary geographically and with time for selected species. Information on local resistance is necessary, especially in the treatment of severe infections. If necessary, expert opinion on the prevalence of local resistance should be obtained in cases where the use of the drug is questioned in at least some infections.

5.2. Pharmacokinetic properties

General properties

Absorption:
Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1 h. The absolute bioavailability is 100%.
Food has little effect on the absorption of levofloxacin.

Distribution:
Approximately 30 - 40% of levofloxacin is bound to serum protein.
Negligible accumulation has been observed with multiple doses of levofloxacin 500 mg daily. There is some accumulation after 500 mg twice daily administration.

Penetration into tissues and body fluids:
Penetration into Bronchial Mucosa, Epithelial Mucus Fluid, and Alveolar Macrophages
After a single 500 mg p.o. dose, maximum levofloxacin concentrations in bronchial mucosa and epithelial mucus fluid were 8.3 microg/ml and 10.9 microg/ml, respectively, and penetration rates from mucosa and epithelial mucus fluid to serum were 1.1-1.8 and 0.8-3, respectively. These levels were reached approximately 1 hour or 4 hours after administration, respectively.

After oral administration of 500 mg and 750 mg for 5 days, mean concentrations in epithelial mucus fluid 4 hours after the last administration were 9.94 mcg/ml and 22.12 mcg/ml, respectively. In alveolar macrophages, they were 97.9 mcg/ml and 105.1 mcg/ml, respectively.

Penetration into Lung Tissue
Maximum concentrations of levofloxacin in lung tissue after a 500 mg p.o. dose were 11.3 µg/g and were reached approximately 4-6 hours after administration, with a lung tissue-to-plasma distribution ratio of 2-5.

Penetration into Bullous Fluid
Maximum concentrations of levofloxacin in bullous fluid of 4 and 6.7 µg/ml were reached 2-4 hours after a 500 mg dose given once or twice daily for 3 days, respectively, with a bullous fluid/plasma ratio of approximately 1.

Distribution into Bone Tissue
Levofloxacin penetrates well into cortical and cancellous tissue in the proximal and distal femur, with penetration rates of 0.1 to 3. The maximum concentration of levofloxacin in the spongiosum proximal femur after 500 mg p.o. is approximately 15.1 microg/g 2 hours after administration.

Penetration into Cerebro-Spinal Fluid
Levofloxacin has low penetration into the cerebro-spinal fluid.

Distribution to prostate tissue
After oral administration of 500 mg levofloxacin 3 times daily, the mean prostate tissue concentration after 2 hours was 8.7 µg/g and the mean prostate/plasma concentration was 1.84.

Concentration in urine
After single oral doses of 150 mg, 300 mg, or 500 mg, the mean urine concentrations of levofloxacin were 44 mg/L, 91 mg/L, and 200 mg/L, respectively.

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

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 total body clearance following a single 500 mg levofloxacin dose was 175 ±29.2 ml/min. The mean total body clearance following a single 750 mg levofloxacin dose was 143 ±29.1 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/Non-linearity:
Levofloxacin obeys linear pharmacokinetics over a range of 150 to 600 mg.

Special populations
Patients with renal insufficiency:
The pharmacokinetics of levofloxacin is 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:

Cl_{cr} [ml/min]	<20	20 - 49	50 – 80
Cl_R [ml/min]	13	26	57
$t_{½}$ [h]	35	27	9

Elderly patients:
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 a 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 mice 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 tumor development in a photocarcinogenicity study.

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

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Crospovidone
Hypromellose 5 CPS
Microcrystalline cellulose
Sodium stearyl fumarate

Film coating (Opadry YS-1-18027 A White):
HPMC 2910/ Hypromellose
Titanium dioxide
Macrogol/PEG
Polysorbate 80

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store at room temperature below 25°C and protect from light.

6.5 Nature and contents of container
Blister of 7 film coated tablets, coated with transparent PVDC on one side and printed aluminum foil on the other. Each cardboard box contains 7 film coated tablets.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER
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