SCHEDULING STATUS: **S4**

PROPRIETARY NAMES AND DOSAGE FORMS:

SANDOZ LEVOFLOXACIN 250 (film-coated tablets)

SANDOZ LEVOFLOXACIN 500 (film-coated tablets)

COMPOSITION:

Each Sandoz Levofloxacin 250 tablet contains levofloxacin hemihydrate equivalent to 250 mg levofloxacin.

Each Sandoz Levofloxacin 500 tablet contains levofloxacin hemihydrate equivalent to 500 mg levofloxacin.

Excipients:

Croscarmellose sodium, ethanol*, glycerol dibehenate, lactose monohydrate, povidone, sodium starch glycolate, talc and coating substances.

*Ethanol evaporates during manufacture and is not included in the final product.

Each Sandoz Levofloxacin 250 tablet contains sugar (lactose monohydrate 13,27 mg).

Each Sandoz Levofloxacin 500 tablet contains sugar (lactose monohydrate 26,54 mg).

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.1 Broad and medium spectrum antibiotics

PHARMACOLOGICAL ACTION:

Levofloxacin is a broad spectrum bactericidal agent from the chemical group fluoroquinolone. Levofloxacin is the pure (-) (S) enantiomer of ofloxacin.

Mechanism of action:

Levofloxacin's bactericidal action results from interference with the enzymes topoisomerase IV and DNA gyrase, which are needed for the DNA replication, transcription, repair and recombination.

Levofloxacin is bactericidal *in vitro*. Cross-resistance exists between levofloxacin and other fluoroquinolone *in vitro*. Generally there is no cross-resistance between levofloxacin and other classes of antibacterial agents, due to the mechanism of action of levofloxacin.

The antibacterial spectrum of levofloxacin covers many Gram-positive and Gram-negative bacteria.

Gram-negative organisms:

Acinetobacter calcoaceticus, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Proteus mirabilis and *Pseudomonas aeruginosa*.

Gram-positive organisms:

Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes and *Streptococcus faecalis*.

Other organisms:

Chlamydia pneumoniae, Legionella pneumophila and *Mycoplasma pneumoniae*.
In vitro sensitivity does not necessarily imply *in vivo* efficacy.

Pharmacokinetic properties:

Absorption:

After oral administration levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1 hour. Food has little effect on the absorption of levofloxacin and the tablets may be taken during or between meals. The absolute bioavailability is approximately 100 %.

Distribution, metabolism and excretion:

Levofloxacin is approximately 30 to 40 % bound to serum protein. Steady-state is achieved within three days.

Levofloxacin is metabolised to a small degree to inactive metabolites being desmethyllevofloxacin and levofloxacin-N-oxide. The elimination half-life of levofloxacin is six to eight hours after oral and intravenous administration. Levofloxacin is excreted largely unchanged, primarily via the kidneys.

Distribution in tissues and fluids:

Levofloxacin penetrates well into lung tissue, bone tissue, bronchial mucosa, epithelial lining fluid and blister fluid.

INDICATIONS:

SANDOZ LEVOFLOXACIN can be used in adults, in the treatment of the following bacterial infections:

Acute exacerbations of chronic bronchitis:

Caused by *H. influenzae, K. pneumoniae, S. aureus, M. catarrhalis, E. coli, H. parainfluenzae* or *S. pneumoniae*.

Pneumonia (community acquired):

Caused by *H. influenzae, S. pneumoniae, S. aureus, M. catarrhalis, H. parainfluenzae, K. pneumoniae, E. coli, Mycoplasma pneumoniae, Chlamydia pneumoniae* or *Legionella pneumophila*.

Sinusitis:

Caused by *H. influenzae, S. pneumoniae, S. aureus, M. catarrhalis* or *H. parainfluenzae*.

Urinary tract infections (complicated) and acute pyelonephritis:

Caused by *E. coli, K. pneumoniae, S. faecalis, P. mirabilis, Enterobacter cloacae* and *P. aeruginosa*.

Uncomplicated urinary tract infections in women:

Caused by *E. coli, K. pneumoniae*.

Skin and soft tissue infections (uncomplicated):

Caused by *S. aureus, S. pyogenes, Acinetobacter calcoaceticus, E. cloacae, P. mirabilis, P. aeruginosa, E. coli, K. pneumoniae* or *S. faecalis*.

Skin and soft tissue infections (complicated):

Caused by *S. aureus, S. pyogenes, P. mirabilis, E. coli, K. pneumoniae, S. faecalis, E. cloacae, K. oxytoca*.

Intra-abdominal infections:

Caused by *E. coli* and anaerobic micro-organisms.

CONTRAINDICATIONS:

The use of SANDOZ LEVOFLOXACIN is contraindicated in:

- Patients with previous hypersensitivity reaction to levofloxacin, other quinolones, or any other ingredient.
- Epilepsy.
- Patients with history of tendon disorders associated with fluoroquinolone administration.
- Children or adolescents (under 18 years of age).
- During pregnancy and lactation.

WARNINGS AND SPECIAL PRECAUTIONS:

SANDOZ LEVOFLOXACIN SHOULD NOT BE GIVEN TO PATIENTS UNDER 18 YEARS OF AGE.

Caution should be exercised when using SANDOZ LEVOFLOXACIN in patients:

- prone to seizures, such as patients with pre-existing central nervous system lesions,
- being treated with fenbufen or other non-steroidal anti-inflammatory medicines or using medicines which lower the cerebral seizure threshold, such as theophylline,
- driving or operating machinery as the use of SANDOZ LEVOFLOXACIN may alter the ability to drive or to operate machinery,

- being tested for tuberculosis as SANDOZ LEVOFLOXACIN inhibits the growth of *Mycobacterium tuberculosis* and therefore may give false-negative results in the bacteriological diagnosis of tuberculosis,
- exposed to ultraviolet light such as sunlight through window glass or longer wavelength ultraviolet (UVA) from sunbeds, in order to prevent photosensitisation.

Lactose intolerance:

Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take SANDOZ LEVOFLOXACIN.

SANDOZ LEVOFLOXACIN contains lactose monohydrate which may have an effect on the glycaemic control of patients with diabetes mellitus.

INTERACTIONS:

The absorption of SANDOZ LEVOFLOXACIN is significantly reduced when administered with iron salts, antacids and sucralfate. It is recommended that preparations containing iron salts, sucralfate, magnesium- or aluminium-containing antacids should not be taken 2 hours before or after SANDOZ LEVOFLOXACIN administration.

SANDOZ LEVOFLOXACIN is known to inhibit hepatic medicine metabolism and may interfere with the clearance of medicines, such as theophylline, fenbufen or similar non-steroidal anti-inflammatory medicines that lower the seizure threshold.

PREGNANCY AND LACTATION:

The use of SANDOZ LEVOFLOXACIN during pregnancy is contraindicated.

DOSAGE AND DIRECTIONS FOR USE:

SANDOZ LEVOFLOXACIN tablets should be swallowed whole, without crushing. SANDOZ LEVOFLOXACIN tablets may be taken on an empty stomach or with meals.

SANDOZ LEVOFLOXACIN is to be taken once or twice daily in a usual dose of 250 or 500 mg. The dosage will depend on the type of pathogen and the severity of the infection. The use of SANDOZ LEVOFLOXACIN should be continued for a minimum of 48 to 72 hours after commencement of treatment. The duration of therapy varies according to the course of the disease.

The following daily dose are recommended for SANDOZ LEVOFLOXACIN:

Daily dosage recommended in patients with normal renal function:

Bronchitis, bacterial exacerbations:

500 mg once daily for 5 to 10 days.

Pneumonia, community acquired:

500 mg once or twice daily for 10 to 14 days. (The higher dosage should be chosen in the presence of complicating factors e.g. co-morbidity, advanced age).

Sinusitis:

500 mg once daily for 10 to 14 days.

Urinary tract infections, (complicated) and acute pyelonephritis:

250 mg once daily for 10 days.

Urinary tract infections (uncomplicated) in women:

250 mg once daily for 3 days.

Uncomplicated skin and soft tissue infections:

250 to 500 mg once daily for 7 to 10 days.

Complicated skin and soft tissue infections:

500 mg once daily for 10 to 14 days.

Intra-abdominal infections:

500 mg once daily in combination with an antibiotic with anaerobic coverage for 10 to 14 days.

Above indications when bacteraemia or septicaemia is present:

500 mg twice daily for 10 to 14 days.

Daily dosage recommended in patients with impaired renal function:

Dosage must be adjusted in patients with impaired renal function according to the degree of impairment (creatinine clearance ≤ 50 mℓ/min):

Patients with a creatinine clearance between 20 and 50 mℓ/min:

Patients meant to be taking 250 or 500 mg once daily: a normal single dose should be given initially and then reduced by half this dose once daily.

Patients meant to be taking 500 mg twice daily: the initial dose should be 500 mg and then 250 mg should be taken twelve hourly.

Patients with a creatinine clearance between 10 and 19 mℓ/min:

Patients meant to be taking 250 mg once daily: a normal single dose should be given initially and then reduced to 125 mg every 48 hours.

Patients meant to be taking 500 mg once daily: should be given a normal single dose initially and then this dose should be reduced to 125 mg every 24 hours.

Patients meant to be taking 500 mg twice daily: should be given 500 mg initially and then this dose should be reduced to 125 mg every 12 hours.

Patients with a creatinine clearance of less than 10 mℓ/min or in patients on haemodialysis or CAPD (Continuous Ambulatory Peritoneal Dialysis):

In patients where the prescribed dosage is 250 mg once daily: a normal single dose should be given initially and then this dose should be reduced to 125 mg every 48 hours.

Patients meant to be taking 500 mg once daily: should be given a normal single dose initially and then this dose should be reduced to 125 mg every 24 hours.

Patients meant to be taking 500 mg twice daily: should be given 500 mg initially and then this dose should be reduced to 125 mg every 24 hours.

No adjustment of dosage is required in the elderly or in patients with impaired liver function.

SIDE EFFECTS:

The following side effects have been reported.

Gastrointestinal disorders:

Frequent: Gastrointestinal symptoms may occur (gastric or abdominal symptoms, loss of appetite, nausea, vomiting, and diarrhoea).

Less frequent: The onset of diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with SANDOZ LEVOFLOXACIN may indicate the appearance of pseudomembranous colitis. Suspicion of pseudomembranous colitis requires immediate cessation of treatment with appropriate specific antibiotic therapy.

Nervous system disorders:

Frequent: Disturbance of the nervous system, e.g. headaches, dizziness, sleep disturbances, unsteady gait and numbness and tingling in the limbs (paraesthesiae), visual and auditory disturbances, disturbances of the senses of taste and smell.

Less frequent: Tremor (disturbances of muscular co-ordination), hallucinations, convulsions and psychotic reactions such as restlessness, agitation, anxiety, depression and confusion.

In the event of such adverse reactions, SANDOZ LEVOFLOXACIN must be discontinued immediately and the medical practitioner informed.

Blood and the lymphatic system disorders:

Less frequent: Changes in the blood picture (leucopenia, eosinophilia, neutropenia, agranulocytosis, thrombocytopenia, pancytopenia, and haemolytic anaemia) have been reported.

Hepato-biliary disorders:

Less frequent: Hepatitis and transient increase in liver enzymes and/or bilirubin and in serum creatinine have been observed.

Renal and urinary disorders:

Less frequent: Interstitial nephritis and acute kidney failure may also occur.

Skin and subcutaneous tissue disorders:

Less frequent: Photosensitivity reactions (skin reactions on exposure to strong sunlight and artificial UV rays) have been reported.

Immune system disorders:

Frequent: Allergic manifestations may occur, in particular hypersensitivity reactions of the skin such as pruritus, rash, urticaria and vasculitis. Isolated cases of severe bullous eruptions such as Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) and erythema exsudativum multiforme have been reported.

Musculoskeletal, connective tissue disorders:

Less frequent: Tendinitis (e.g. Achilles tendon) is observed with quinolones and corticosteroids, and if it is suspected, treatment with SANDOZ LEVOFLOXACIN must be stopped immediately and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

Other musculoskeletal side effects such as arthralgia and myalgia have been observed and include:

- Tendon rupture (Achilles tendon).
- Muscular weakness, which may be of special importance in patients with myasthenia gravis.
- Isolated cases of rhabdomyolysis.

Endocrine disorders:

Less frequent: Hypoglycaemia, especially in diabetics, may occur.

General disorders:

Frequent: Asthenia, fungal overgrowth and proliferation of other resistant micro-organisms may occur.

SANDOZ LEVOFLOXACIN is known to possibly trigger attacks of porphyria in patients suffering from porphyria.

Less frequent: There have been symptoms such as fever, allergic pneumonitis, angio-oedema, hypotension and anaphylactic-like shock. In the event of such reactions, SANDOZ LEVOFLOXACIN should be discontinued immediately. Medical treatment (therapy for shock) is imperative.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

The symptoms that can be expected from an acute overdosage of SANDOZ LEVOFLOXACIN are central nervous system symptoms such as confusion, dizziness, impairment of consciousness and convulsive seizures. The treatment of an overdosage is only symptomatic and supportive. SANDOZ LEVOFLOXACIN is not effectively removed by haemodialysis or peritoneal dialysis.

IDENTIFICATION:

Sandoz Levofloxacin 250: Light orange-pink coloured, octagonal, biconvex, film-coated tablet, scored on both sides.

Sandoz Levofloxacin 500: Light orange-pink coloured, octagonal, biconvex, film-coated tablet, scored on one side.

PRESENTATIONS:

Sandoz Levofloxacin 250: film-coated tablets, packed in PVC/TE/PVDC/Al blister packs of 3 or 5 tablets. One side of the blister pack is transparent and the other side is silver coloured.

Sandoz Levofloxacin 500: film-coated tablets, packed in PVC/TE/PVDC/Al blister packs of 5 or 10 tablets. One side of the blister pack is transparent and the other side is silver coloured.

STORAGE INSTRUCTIONS:

Store at or below 25 °C in a dry place. Keep in the pack until required for use. Protect from moisture and light.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS:

Sandoz Levofloxacin 250: A40/20.1.1/0525

Sandoz Levofloxacin 500: A40/20.1.1/0526

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:

Sandoz SA (Pty) Ltd[1]

72 Steel Road

Spartan

Kempton Park

1619

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

Date of registration: 06 October 2006

Date of most recent approval of professional information: 17 April 2009

Additional countries registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Botswana	Sandoz Levofloxacin 250 (3 tablets)	S2	BOT1302262
	Sandoz Levofloxacin 250 (5 tablets)	S2	BOT1302262A
	Sandoz Levofloxacin 500 (5 tablets)	S2	BOT1302264
	Sandoz Levofloxacin 500 (10 tablets)	S2	BOT1302264A
Namibia	Sandoz Levofloxacin 250	NS2	07/20.1.1/0111
	Sandoz Levofloxacin 500	NS2	07/20.1.1/0112
Zambia	Sandoz Levofloxacin 250	POM	039/051
	Sandoz Levofloxacin 500	POM	039/050

ATC code: J01MA12 - Fluoroquinolones

Name and address of manufacturer:

Lek Pharmaceuticals d.d.

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[1]Company Reg. No.: 1990/001979/07