Approved Professional Information for Medicines for Human Use:

AUSTELL-LEVOFLOXACIN 250/500 mg

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AUSTELL–LEVOFLOXACIN 250 mg film-coated tablets

AUSTELL–LEVOFLOXACIN 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AUSTELL–LEVOFLOXACIN 250 mg:

Each film-coated tablet contains levofloxacin hemihydrate equivalent to levofloxacin 250 mg.

AUSTELL–LEVOFLOXACIN 500 mg:

Each film-coated tablet contains levofloxacin hemihydrate equivalent to levofloxacin 500 mg.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

AUSTELL-LEVOFLOXACIN 250 mg:

Pink coloured, capsule shaped, biconvex, film-coated tablets with a breakline on both the sides.

AUSTELL-LEVOFLOXACIN 500 mg:

Pink coloured, capsule shaped, biconvex, film-coated tablets with a breakline on both the sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AUSTELL-LEVOFLOXACIN is indicated for the treatment of severe and/or complicated infections caused by levofloxacin sensitive bacteria where other antimicrobials, approved for a similar indication and to which the causative bacteria are sensitive, were considered not to be an appropriate treatment option, have failed, are contraindicated or not tolerated.

AUSTELL-LEVOFLOXACIN is not indicated/approved for the initiation of treatment (first line treatment) of infections described as mild/moderate/acute and uncomplicated, caused by bacteria sensitive to levofloxacin, unless treatment with other appropriate antimicrobials, approved for a similar indication and to which the causative bacteria are sensitive, have failed, are contraindicated or not tolerated.

AUSTELL-LEVOFLOXACIN tablets are indicated for the treatment of the following bacterial infections, where these infections are compliant with the indication context:

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

- **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.*
- **bacterial sinusitus**: 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*.
- **skin and soft tissue infections**: caused by *S. aureus, S. pyogenes, Acinetobacter calcoaceticus, E. cloacae, P. mirabilis, P. aeruginosa, E. coli, K. pneumoniae or S. faecalis.*
- **complicated skin and soft tissue infections**: 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.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to AUSTELL-LEVOFLOXACIN. Therapy with AUSTELL-LEVOFLOXACIN may be initiated in severe and/or complicated infections before results of these tests are known; once results become available, appropriate therapy should be continued.

4.2 Posology and method of administration

Posology

The dosage range is 250 – 750 mg twice daily. The duration of treatment to contain and eradicate infection depends upon the type and severity of the infection, immunological status, clinical response and bacteriological findings. Use the lowest effective dose for the shortest time to contain and eradicate the infection.

The following daily doses are recommended for AUSTELL LEVOFLOXACIN:

Daily dosage recommended in patients with normal renal function:

Bronchitis, bacterial exacerbations: 500 mg once daily for 5 – 10 days.

Pneumonia, community acquired: 500 mg once or twice daily for 10 - 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.

Complicated skin and soft tissue infections: 500 mg once daily for 10 – 14 days.

Intra-abdominal infections*:* 500 mg once daily in combination with an antibiotic with anaerobic coverage for 10 - 14 days.

Above interactions when bacteraemia or septicaemia is present: 500 mg twice daily for 10 – 14 days.

Daily dosage recommended in patient 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 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 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 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 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 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 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 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**.**

Method of administration

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

4.3 Contraindications

The use of AUSTELL-LEVOFLOXACIN is contraindicated in:

- Previous hypersensitivity reaction to levofloxacin, other quinolones, or any other ingredient in the formulation.
- Epilepsy.
- Children or adolescents (under 18 years of age).
- During pregnancy and lactation.
- Concomitant use of levofloxacin with other medicines known to prolong the QT interval, or in patients with disorders that prolong the QT interval to such an extent that it leads to

prolonged QTcF interval known to be associated with serious and potentially fatal dysrhythmias or if symptomatic dysrhythmias occur with concomitant use at time intervals shorter than QT intervals usually associated with dysrhythmias.

- A history of tendon, muscle, joint, nerve, central nervous system, epilepsy or psychotic disorders especially those related to previous quinolone/fluoroquinolone use where alternative, appropriate antibiotic choices are available for treatment. (see section 4.4).
- Myasthenia gravis where alternative appropriate antibiotic choices are available to treat these patients (see section 4.4).
- Aortic aneurysm and/or dissection or in patients with risk factors or conditions predisposing for aortic aneurysm and/or dissection if alternative appropriate antibiotic choices are available (see section 4.4).
- Concomitant use of fluoroquinolones with angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) in patients with moderate to severe renal impairment and in the elderly (see section 4.4 and 4.5).
- Patients with confirmed mitral valve and/aortic valve regurgitation unless no safer appropriate alternative antibiotic is available, has failed of is not well tolerated.

4.4 Special warnings and precautions for use

Severe infections and infections due to Gram positive or anaerobic bacteria

AUSTELL-LEVOFLOXACIN should not be used in staphylococcal infections and infections involving anaerobic bacteria.

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.

Clostridium difficile-associated disease

Diarrhoea, particularly if severe, persistent, and/or bloody, during or after treatment with Levofloxacin (including several weeks after treatment), may be symptomatic of *Clostridium difficile*-associated disease (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis (see section 4.8). It is therefore important to consider this diagnosis in patients who develop serious diarrhoea during or after treatment with levofloxacin. If CDAD is suspected or confirmed, Levofloxacin Tablets should be stopped immediately, and appropriate treatment initiated without delay (e.g. oral metronidazole or vancomycin). Medicinal products inhibiting the peristalsis are contraindicated in this clinical situation.

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.

Hypersensitivity reactions

Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema to anaphylactic shock), occasionally following the initial dose (see section 4.8). Patients should

discontinue treatment immediately and contact their physician or an emergency physician, who will initiate appropriate emergency measures.

Severe bullous reactions

Cases of severe bullous skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with levofloxacin (see section 4.8). 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 (see section 4.8).

Prevention of photosensitisation

Photosensitisation has been reported with levofloxacin (see section 4.8). 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 to prevent photosensitisation.

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 medicines are given concomitantly (see section 4.5).

Patients with renal impairment

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

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 (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.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see sections 4.7 and 4.8).

Cardiac disorders

Aortic aneurysm and dissection

There is some evidence of an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the elderly population. Fluoroquinolones, such as, LEVOFLOXACIN should only be used in patients at risk if no other treatment options are available (see section 4.3).

Therefore, fluoroquinolones, such as LEVOFLOXACIN should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a medical practitioner in an emergency department.

QT interval prolongation

AUSTELL-LEVOFLOXACIN has been associated with QT prolongation.

Concomitant use of AUSTELL-LEVOFLOXACIN with medicines or in patients with disorders that can result in prolongation of the QT interval is contraindicated if concomitant use leads to prolongation of QTc interval associated with serious or potentially fatal dysrhythmias or symptomatic dysrhythmias occur at QTc intervals less than usually associated with dysrhythmias such as, for example:

- concomitant use of medicines that are known to prolong the QT interval (e.g. Class IA and III antidysrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.5)
- congenital long QT syndrome
- risk of Torsades de Pointes,
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including AUSTELL- LEVOFLOXACIN, in these populations.

A pre-treatment ECG and frequent follow up ECG monitoring is mandatory with concomitant use to determine whether concomitant use is contraindicated. (See sections 4.2, 4.3, 4.5, 4.8 and 4.9).

Mitral valve and aortic regurgitation

There is some evidence, although inconclusive, of a possible association between fluoroquinolone use and mitral valve and/or aortic valve regurgitation. A thorough cardiovascular examination including an echocardiogram, should be performed before oral fluoroquinolones are prescribed. Fluoroquinolones should not be prescribed to patients with mitral valve and or aortic valve regurgitation (see section 4.3).

Concomitant use with ACE inhibitors/angiotensin receptor blockers (ARBs)

Concomitant use of fluoroquinolones, such as AUSTELL-LEVOFLOXACIN**,** with ACE inhibitors/angiotensin receptor blockers (ARBs) may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment with AUSTELL-LEVOFLOXACIN.

Children and adolescents

AUSTELL-LEVOFLOXACIN is contraindicated in children less than 18 years (see section 4.3). In children arthropathy is reported to occur commonly.

Musculoskeletal system

Myasthenia gravis

The use of AUSTELL-LEVOFLOXACIN in patients with myasthenia gravis is contraindicated if alternative appropriate antibiotic choices are available (see section 4.3). Fluoroquinolones, including such as AUSTELL-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.

Tendinitis and tendon rupture

AUSTELL-LEVOFLOXACIN should not be used in patients with a history of tendon disorders, especially those related to previous exposure to quinolone or fluoroquinolone use (see section 4.3).

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided (see section 4.8).
At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with levofloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation).

Corticosteroids should not be used if signs of tendinopathy occur.

Nervous system

Patients predisposed to seizures

Quinolones may lower the seizure threshold and may trigger seizures. such as AUSTELL-LEVOFLOXACIN is contraindicated in patients with a history of epilepsy (see section 4.3). AUSTELL- LEVOFLOXACIN should only be used in patients predisposed to seizures where alternative appropriate therapies have failed, are contraindicated or not tolerated, since these patients are endangered due to possible central nervous system side effects. Cases of status epilepticus have been reported (see sections 4.3 and 4.8).

Patients predisposed to seizures may be patients with pre-existing central nervous system lesions, concomitant treatment with fenbufen and similar non-steroidal anti-inflammatory drugs (NSAIDs) or with medicines which lower the cerebral seizure threshold, such as theophylline (see section 4.5).

If seizures occur levofloxacin should be discontinued (see section 4.8).

Peripheral neuropathy

Sensory or sensorimotor peripheral neuropathy have been reported in patients receiving fluoroquinolones, including levofloxacin, which can be rapid in its onset (see section 4.8). Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.

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 (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.

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 medicines and other forms of interaction

Effect of other medicinal products on levofloxacin

Iron salts, zinc salts, magnesium- or aluminium-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 levofloxacin 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 levofloxacin tablet administration (see section 4.2). Calcium salts have a minimal effect on the oral absorption of levofloxacin.

Sucralfate

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

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

No pharmacokinetic interactions of levofloxacin were found with theophylline in a reported clinical study. However, a pronounced lowering of the cerebral seizure threshold may occur when quinolones are given concurrently with theophylline, nonsteroidal anti-inflammatory medicine, or other agents which lower the seizure threshold.

Levofloxacin concentrations reported 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 medicines can block 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 medicine that effect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

Other relevant information

Documented clinical pharmacology studies have shown that the pharmacokinetics of levofloxacin were not affected to any clinically

relevant extent when levofloxacin was administered together with the following medicine:

- calcium carbonate
- digoxin
- glibenclamide
- ranitidine

Effect of levofloxacin on other medicinal products

Ciclosporin

The half-life of ciclosporin was increased by 33 % when co-administered 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 (see section 4.4).

Medicines known to prolong QT interval

Levofloxacin (also other fluoroquinolones) should be used with caution in patients receiving medicine known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotic). (See section 4.4 QT interval prolongation).

Other relevant information

In a reported 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.

Other forms of interactions

Food

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

Angiotensin converting enzyme (ACE) inhibitors/ angiotensin receptor blockers (ARBs)

Concomitant use of fluoroquinolones, such as AUSTELL-LEVOFLOXACIN, with angiotensin converting enzyme (ACE) inhibitors/ angiotensin receptor blockers (ARBs) may precipitate acute kidney injury in patients with moderate to severe renal impairment (see section 4.3).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data with respect to the use of levofloxacin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). 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 (see sections 4.3 and 5.3).

Breastfeeding

Levofloxacin tablets are contraindicated in breastfeeding 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 breastfeeding women (see sections 4.3 and 5.3).

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

System Organ Class	**Frequent**	**Less frequent**	**Frequency not known (cannot be estimated from available data)****
Infections and infestations		Fungal infection (including Candida Infection)	

		Pathogen resistance	
Blood and lymphatic system disorders		Leukopenia Eosinophilia Thrombocytopenia Neutropenia	Pancytopenia Agranulocytosis Haemolytic anaemia
Immune system disorders		Angioedema Hypersensitivity (see section 4.4)	Anaphylactic shock[a] Anaphylactoid shock [a] (see section 4.4)
Endocrine disorders		Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)	
Metabolism and nutrition disorders		Anorexia Hypoglycaemia particularly in diabetic patients (see section 4.4)	Hyperglycaemia Hypoglycaemic coma (see section 4.4)
Psychiatric disorders	Insomnia	Anxiety Confusional state Nervousness Psychotic reactions	Psychotic disorders with self-endangering behaviour including suicidal ideation or

		(with e.g. hallucination, paranoia) Depression Agitation Abnormal dreams Nightmares	suicide attempt (see section 4.4)
Nervous system disorders	Headache Dizziness	Somnolence Tremor Dysgeusia Convulsion (see sections 4.3 and 4.4) Paraesthesia	Peripheral sensory neuropathy (see section 4.4) Peripheral sensory motor neuropathy (see section 4.4) Parosmia including anosmia Dyskinesia Extrapyramidal disorder Ageusia Syncope Benign intracranial hypertension
Eye disorders		Visual disturbances such as blurred vision (see section 4.4)	Transient vision loss (see section 4.4)

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 (see sections 4.4 and 4.9)
Vascular disorders		Hypotension	
Respiratory thoracic and mediastinal disorders		Dyspnoea	Bronchospasm Pneumonitis allergic
Gastrointestinal disorders	Diarrhoea Vomiting Nausea	Abdominal pain Dyspepsia Flatulence Constipation	Diarrhoea – haemorrhagic which in very rare cases may be indicative of enterocolitis, including

			pseudomembranous colitis (see section 4.4) Pancreatitis
Hepatobiliary disorders	Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)	Blood bilirubin increased	Jaundice and severe liver injury, including cases with fatal acute liver failure, primarily in patients with severe underlying diseases (see section 4.4) Hepatitis
Skin and subcutaneous tissue disorders[b]		Rash Pruritus Urticaria Hyperhidrosis	Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Photosensitivity reaction (see section 4.4) Leukocytoclastic vasculitis Stomatitis
Musculoskeletal and connective		Arthralgia Myalgia	Rhabdomyolysis Tendon rupture (e.g. Achilles tendon) (see

tissue disorders*		Tendon disorders (see sections 4.3 and 4.4) including tendinitis (e.g. Achilles tendon) Muscular weakness which may be of special importance in patients with myasthenia gravis (see section 4.4)	sections 4.3 and 4.4) Ligament rupture Muscle rupture Arthritis
Renal and urinary disorders		Blood creatinine increased Renal failure acute (e.g. due to interstitial nephritis)	
General disorders and administration site conditions		Asthenia Pyrexia	Pain (including pain in back, chest, and extremities)

[a] Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose

[b] Mucocutaneous reactions may sometimes occur even after the first dose

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

attacks of porphyria in patients with porphyria.

Post-marketing Experience

Cases of mitral valve and/aortic valve regurgitation were reported in patients treated with oral fluoroquinolones. Due to insufficient post marketing information in the reported cases, it is unknown whether fluoroquinolone use was the causative factor, or a contributory factor or played no role in the reported cases where mitral cases and/or aortic regurgitation was diagnosed.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

According to reported 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 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: Fluoroquinolones

ATC code J01MA12

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

Mechanism of action

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

Pharmacokinetic (PK)/pharmacodynamic (PD) relationship

The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum concentration in serum (C_{max}) or the area under the curve (AUC) and the minimal inhibitory concentration (MIC).

Mechanisms of resistance

Resistance to levofloxacin is acquired through a stepwise process by target site mutations in both type II topoisomerases, DNA gyrase and topoisomerase IV. Other resistance mechanisms such as permeation barriers (common in Pseudomonas aeruginosa) and efflux mechanisms may also affect susceptibility to levofloxacin.

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

Micro-organism ~~S~~species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* *Staphylococcus aureus methicillin-resistant*[#] *Coagulase negative Staphylococcus spp*
Aerobic Gram-negative micro-organisms *Acinetobacter baumannii* *Citrobacter freundii* *Enterobacter aerogenes* *Enterobacter cloacae* *Escherichia coli* *Klebsiella pneumoniae*

Morganella morganii *Proteus mirabilis* *Providencia stuartii* *Pseudomonas aeruginosa* *Serratia marcescens*
Anaerobic micro-organisms *Bacteroides fragilis*
Inherently resistant strains
Aerobic Gram-positive micro-organisms *Enteroccus faecium*

5.2 Pharmacokinetic properties

Absorption

Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1- 2 h. The absolute bioavailability is 99- 100 %.
Food has little effect on the absorption of levofloxacin.
Steady state conditions are reached within 48 hours following a 500 mg once or twice daily dosage regimen.

Distribution

Approximately 30 - 40 % of levofloxacin is bound to serum protein. The mean volume of distribution of levofloxacin is
approximately 100 l after single and repeated 500 mg doses, indicating widespread distribution into body tissues.
Penetration into tissues and body fluids:

Levofloxacin has been shown to penetrate into bronchial mucosa*,* epithelial lining fluid, alveolar macrophages, lung

tissue*, skin (*blister fluid*), prostatic tissue and urine. However, levofloxacin has* poor penetration 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 excreted in urine. Levofloxacin is stereochemically stable and does not undergo chiral inversion.

Elimination

Following oral and intravenous administration of levofloxacin, it is eliminated relatively slowly from the plasma (t½: 6 - 8h). Excretion is primarily by the renal route > 85 % of the administered dose).

The mean apparent total body clearance of levofloxacin following a 500 mg single dose was 175 +/-29.2 ml/min.

There are no major differences in the pharmacokinetics of levofloxacin following intravenous and oral administration, suggesting that the oral and intravenous routes are interchangeable.

Linearity

Levofloxacin obeys linear pharmacokinetics over a range of 50 to 1000 mg.

Special populations

Patients with renal insuffiency

The pharmacokinetics of levofloxacin are affected by renal impairment. With decreasing renal function renal elimination and clearance are decreased, and elimination half-lives increased as shown in the table below:

Pharmacokinetics in renal insufficiency following single oral 500 mg dose

Cl_{cr} [ml/min]	<20	20 - 49	50 - 80
Cl_R [ml/min]	13	26	57
$t_{1/2}$ [h]	35	27	9

Elderly patients

There are no significant differences in levofloxacin kinetics between young and elderly patients, except those associated with differences in creatinine clearance.

Gender differences

Separate analysis for male and female patients showed small to marginal gender differences in levofloxacin pharmacokinetics. There is no evidence that these gender differences are of clinical relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The other ingredients are crospovidone, hydroxypropyl microcrystalline cellulose, ferric oxide red, ferric oxide yellow, methyl cellulose, polyethylene glycol, purified talc, sodium stearyl fumarate, titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a dry place at or below 25°C. Protect from light.

Keep blister packs in carton until required for use.

KEEP OUT OF THE REACH OF CHILDREN

6.5 Nature and contents of container

AUSTELL-LEVOFLOXACIN 250 mg:

Blister pack (Clear PVC film and Aluminium foil) of 1 x 3, 1 x 5, 1 x 10 and 2 x 14 tablets.

AUSTELL-LEVOFLOXACIN 500 mg:

Blister pack (Clear PVC film and Aluminium foil) of 1 x 5 and 1 x 10 and 2 x 14 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBER(S)

AUSTELL-LEVOFLOXACIN 250 mg: 41/20.1.1/1018

AUSTELL-LEVOFLOXACIN 500 mg: 41/20.1.1/1019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 August 2009

10. DATE OF REVISION OF THE TEXT

08 July 2020