Approved Professional Information for Medicines for Human Use:

LEVOFLOXACIN IV 5 mg/mL AUSTELL

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

LEVOFLOXACIN IV 5 mg/mL AUSTELL Solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mL LEVOFLOXACIN IV 5 mg/mL AUSTELL vial contains levofloxacin hemihydrate equivalent to 500 mg (5 mg/mL) levofloxacin.

100 mL of LEVOFLOXACIN IV 5 mg/mL AUSTELL contain 15,4 mmoL (354,2 mg) sodium.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

LEVOFLOXACIN IV 5 mg/mL AUSTELL Solution for infusion

Clear, odourless, light yellow to greenish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In adults, treatment of bacterial infections due to levofloxacin-susceptible micro-organisms:

- **Acute sinusitis** caused by *H. influenzae*, *S. pneumoniae*, methicillin-sensitive *S. aureus*, *M. catarrhalis* and *H. parainfluenzae*.
- **Acute exacerbations of chronic bronchitis** caused by *H. influenzae*, *K. pneumoniae,* methillin-sensitive *S. aureus*, *M. catarrhalis*, *E. Coli*, *H. parainfluenzae* and *S. pneumoniae.*

- **Community acquired pneumonia** caused by *H. influenzae*, *S. pneumoniae*, methicillin-sensitive *S. aureus, M. catarrhalis, H. parainfluenzae, K. pneumoniae, E. coli*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila*.
- **Chronic Bacterial Prostatitis** caused by *Escherichia coli, Enterococcus faecalis, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus agalactiae, Streptococcus mitis.*
- **Complicated urinary tract infections and acute pyelonephritis** caused by *E. coli, K. pneumoniae, S. faecalis, P. mirabilis, Enterobacter cloacae, P. aeruginosa.*
- **Uncomplicated urinary tract infections in women** caused by *E. coli.*
- **Uncomplicated skin and skin structure infections** caused by methicillin-sensitive *S. aureus, S. pyogenes, Acinetobacter calcoaceticus, E. cloacae, P. mirabilis, P. aeruginosa, E. coli, K. pneumoniae, S. faecalis.*
- **Complicated skin and skin structure infections** caused by methicillin-sensitive *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.

4.2 Posology and method of administration

Posology

LEVOFLOXACIN IV 5 mg/mL AUSTELL is administered once or twice daily.

The dosage depends on the type and severity of infection and sensitivity of the presumed causative pathogen. The duration of therapy varies according to the course of the disease.

LEVOFLOXACIN IV 5 mg/mL AUSTELL should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

LEVOFLOXACIN IV 5 mg/mL AUSTELL daily dose recommendations:

Recommended daily dosage in patients with normal renal function:

- **Acute sinusitis** caused by *H. influenzae*, *S. pneumoniae*, methicillin-sensitive *S. aureus*, *M. catarrhalis* and *H. parainfluenzae*: 500 mg once daily for 10 days.
- **Acute exacerbations of chronic bronchitis** caused by *H. influenzae*, *K. pneumoniae,* methicillin-sensitive S*. aureus*, *M. catarrhalis*, *E.coli*, *H. parainfluenzae* and *S. pneumoniae*: 500 mg once daily for 5 - 10 days.
- **Community acquired pneumonia** caused by *H. influenzae*, *S. pneumoniae*, methicillin-sensitive *S. aureus, M. catarrhalis*, H. parainfluenzae, *K. pneumoniae, E. coli, Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila*: 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).
- **Chronic Bacterial Prostatitis** caused by *Escherichia coli, Enterococcus faecalis, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus agalactiae, Streptococcus mitis*: 500 mg once a day for 28 days.
- **Complicated urinary tract infections and acute pyelonephritis** caused by *E. coli, K. pneumoniae, S. faecalis, P. mirabilis, Enterobacter cloacae, P. aeruginosa*: 250 mg once daily for 10 days.
- **Uncomplicated urinary tract infections in women** caused by *E. coli*: 250 mg once daily for 3 days.
- **Uncomplicated skin and skin structure infections** caused by methicillin-sensitive *S. aureus, S. pyogenes, Acinetobacter calcoaceticus, E. cloacae, P. mirabilis, P. aeruginosa, E.coli, K. pneumoniae, S. faecalis*: 250 to 500 mg once daily for 7 - 10 days.
- **Complicated skin and skin structure infections** caused by methicillin-sensitive *S. aureus, S. pyogenes, P. mirabilis, E. coli, K. pneumoniae, S. faecalis, E. cloacae, K. oxytoca*: 500 mg twice daily for 10 - 14 days.
- **Intra-abdominal infections** caused by *E. coli* and anaerobic micro-organisms: 500 mg once daily in combination with an antibiotic with anaerobic coverage for 10 -14 days.

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

It is usually possible to switch from initial intravenous treatment to the oral route after a few days, according to the condition of the patient. Given the bioequivalence of the parenteral and oral forms, the same dosage can be used.

Special populations

Recommended daily dosage in patients with renal impairment

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

Creatinine clearance between 20 and 50 mL/min:

In patients meant to be taking 250 or 500 mg once daily, a normal single dose should be given initially; and then reduced by half the dose once daily.

If the patient is meant to be taking 500 mg twice daily, the initial dose should be 500 mg and then 250 mg should be administered twelve hourly.

Creatinine clearance between 10 and 19 mL/min:

In 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 the dose should be reduced to 125 mg every 12 hours.

Creatinine clearance of less than 10 mL/min or in patients on haemodialysis or CAPD (Continuous Ambulatory Peritoneal Dialysis):

If 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 the 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 the dose should be reduced to 125 mg every 24 hours.

Liver impairment

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

Paediatric population

LEVOFLOXACIN IV 5 mg/mL AUSTELL is contraindicated in children and adolescents under the age of 18 years.

Elderly population

No dosage adjustment is required in the elderly.

Method of administration

LEVOFLOXACIN IV 5 mg/mL AUSTELL solution for infusion should be infused slowly over a period of not less than 30 minutes for a dosage of 250 mg. LEVOFLOXACIN IV 5 mg/mL AUSTELL solution for infusion should be infused slowly over a period of not less than 60 minutes for a dosage of 500 mg.
For instructions on dilution of LEVOFLOXACIN IV 5 mg/mL AUSTELL before administration, see section 6.6.
For incompatibilities, see section 6.2; for compatibility with other infusion solutions, see section 6.6.

4.3 Contraindications

- Hypersensitivity to levofloxacin, other quinolones, or to any of the excipients of LEVOFLOXACIN IV 5 mg/mL AUSTELL listed in section 6.1.
- Epilepsy (see section 4.4)
- Patients with confirmed mitral valve and/or aortic valve regurgitation unless no safer appropriate alternative antibiotic is available, has failed, or is not well tolerated

- Children or adolescents (see section 4.4)
- Pregnancy and lactation (See section 4.6)
- A history of tendon disorders related to fluoroquinolone, including LEVOFLOXACIN IV 5 mg/mL AUSTELL administration.
- Concomitant use of fluoroquinolones with angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) in patients with moderate to severe renal impairment (creatinine clearance ≤ 30 mL/min) and in elderly patients (see section 4.4 and 4.5).

4.4 Special warnings and precautions for use

Prescribers should adhere to the principles of antibiotic stewardship.

LEVOFLOXACIN IV 5 mg/mL AUSTELL SHOULD NOT BE GIVEN TO PATIENTS UNDER THE AGE OF 18 YEARS (see section 4.3).

The use of levofloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing medicines (see section 4.8). Treatment of these patients with levofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit / risk assessment (see also section 4.3).

Prolonged, disabling and potentially irreversible serious adverse drug reactions

Cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. LEVOFLOXACIN IV 5 mg/mL AUSTELL should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their medical practitioner for advice.

MRSA infections

Methicillin-resistant Staphylococcus aureus (MRSA) are very likely to possess co-resistance to fluoroquinolones, including levofloxacin. Therefore, LEVOFLOXACIN IV 5 mg/mL AUSTELL is not recommended for the treatment of known or suspected MRSA infections unless laboratory results have confirmed susceptibility of the organism to levofloxacin (and commonly recommended antibacterial medicines for the treatment of MRSA infections are considered inappropriate).

Resistance to fluoroquinolones of *E. Coli* – the most common pathogen involved in urinary tract infections – varies. Medical practitioners are advised to take into account the local prevalence of resistance in *E. Coli* to fluoroquinolones.

Infusion time

The recommended infusion time of at least 30 minutes for 250 mg or 60 minutes for 500 mg of LEVOFLOXACIN IV 5 mg/mL AUSTELL should be observed. It is known for ofloxacin that during infusion tachycardia and a temporary decrease in blood pressure may develop. In certain cases, as a consequence of a profound drop in blood pressure, circulatory collapse may occur. Should a conspicuous drop in blood pressure occur during infusion of LEVOFLOXACIN IV 5 mg/mL AUSTELL, the infusion must be halted immediately.

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. Therefore, fluoroquinolones such as levofloxacin as in LEVOFLOXACIN IV 5 mg/mL AUSTELL 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 aortic 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 of a hospital.

QT interval prolongation

Caution should be taken when using fluoroquinolones, including levofloxacin as in LEVOFLOXACIN IV 5 mg/mL AUSTELL, in patients with known risk factors for prolongation of the QT interval such as, for example:

- Concomitant use of medicines that are known to prolong the QT interval (e.g. Class IA or III antidysrhythmics, tricyclic antidepressants, macrolides, antipsychotics), (see section 4.5)
- Congenital long QT syndrome
- Risk of Torsades de Pointes
- Uncorrected electrolyte imbalance such as hypokalaemia or hypomagnesaemia
- Cardiac disease such as heart failure, myocardial infarction, or bradycardia

Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including LEVOFLOXACIN IV 5 mg/mL AUSTELL, in these populations.

Mitral valve and/or aortic valve 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 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 LEVOFLOXACIN IV 5 mg/mL AUSTELL, 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 LEVOFLOXACIN IV 5 mg/mL AUSTELL or ACE inhibitors/renin-angiontensin receptor blockers whether used separately and/or concomitantly.

Musculoskeletal system

Tendinitis and tendon rupture

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 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 with LEVOFLOXACIN IV 5 mg/mL AUSTELL should be avoided (see section 4.2).

At the first sign of tendinitis (e.g. painful swelling, inflammation) treatment with LEVOFLOXACIN IV 5 mg/mL AUSTELL 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 (see sections 4.3 and 4.8).

Exacerbation of myasthenia gravis

Fluoroquinolones, including levofloxacin, as in LEVOFLOXACIN IV 5 mg/mL AUSTELL, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia

gravis. Post-marketing serious adverse reactions, including deaths and the requirement for respiratory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. LEVOFLOXACIN IV 5 mg/mL AUSTELL is not recommended in patients with a known history of myasthenia gravis.

Nervous system

Patients predisposed to seizures

Quinolones may lower the seizure threshold and may trigger seizures. LEVOFLOXACIN IV 5 mg/mL AUSTELL is contraindicated in patients with a history of epilepsy (see section 4.3) and, as with other quinolones, should be used with extreme caution in patients with a known or suspected central nervous system disorder that may predispose them to seizures, or to lower seizure thresholds (e.g. severe cerebral arteriosclerosis), or concomitant treatment with medicines which lower the cerebral seizure threshold, such as fenbufen and similar non-steroidal anti-inflammatory drugs (NSAIDs) and theophylline (see section 4.5). In case of convulsive seizures, (see section 4.8), treatment with LEVOFLOXACIN IV 5 mg/mL AUSTELL should be discontinued.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones including levofloxacin as in LEVOFLOXACIN IV 5 mg/mL AUSTELL, which can be rapid in its onset, can be rapidly progressive and in some cases can be irreversible (see section 4.8). Patients under treatment with LEVOFLOXACIN IV 5 mg/mL AUSTELL should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop, LEVOFLOXACIN IV 5 mg/mL AUSTELL should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of potentially irreversible condition (see section 4.8).

Psychiatric side effects

Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin as in LEVOFLOXACIN IV 5 mg/mL AUSTELL. In certain cases these have progressed to suicidal thoughts and self-endangering behaviour - sometimes after only a single dose of levofloxacin as in LEVOFLOXACIN IV 5 mg/mL AUSTELL (see section 4.8). In the event that the patient develops these reactions, LEVOFLOXACIN IV 5 mg/mL AUSTELL should be discontinued and appropriate measures instituted. Caution is recommended if LEVOFLOXACIN IV 5 mg/mL AUSTELL is to be used in psychotic patients or in patients with history of psychiatric disease.

Interference with laboratory tests

In patients treated with LEVOFLOXACIN IV 5 mg/mL AUSTELL, determination of opiates in urine may give false-positive results. It may be necessary to confirm positive opiate screens by more specific method.

Levofloxacin as in LEVOFLOXACIN IV 5 mg/mL AUSTELL 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 IV 5 mg/mL AUSTELL, (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 IV 5 mg/mL AUSTELL.

LEVOFLOXACIN IV 5 mg/mL AUSTELL treatment should be stopped immediately if CDAD is suspected or confirmed, and appropriate treatment initiated without delay. Anti-peristaltic medicines 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 medicines. Therefore, if LEVOFLOXACIN IV 5 mg/mL AUSTELL has to be used in these patients, potential occurrence of haemolysis should be monitored.

Patients with renal impairment

Since levofloxacin is excreted mainly by the kidneys, doses of LEVOFLOXACIN IV 5 mg/mL AUSTELL should be adjusted in patients with renal impairment product should be adjusted (see section 4.2).

Hypersensitivity reactions

Levofloxacin as in LEVOFLOXACIN IV 5 mg/mL AUSTELL 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 LEVOFLOXACIN IV 5 mg/mL AUSTELL treatment immediately and contact their medical practitioner or an emergency medical practitioner, 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 as in LEVOFLOXACIN IV 5 mg/mL AUSTELL treatment (see section 4.8). Patients should be advised to contact their medical practitioner immediately prior to continuing treatment with LEVOFLOXACIN IV 5 mg/mL AUSTELL 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 medicine (e.g., glibenclamide) or with insulin and levofloxacin. Cases of hypoglycaemic coma have been reported. In diabetic patients taking LEVOFLOXACIN IV 5 mg/mL AUSTELL, careful monitoring of blood glucose is recommended (see section 4.8).

Prevention of photosensitisation

Photosensitisation has been reported with levofloxacin as in LEVOFLOXACIN IV 5 mg/mL AUSTELL (see section 4.8). It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial ultraviolet (UV) rays (e.g. sunray lamp, solarium), during treatment with LEVOFLOXACIN IV 5 mg/mL AUSTELL and for 48 hours following treatment discontinuation, in order 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 as in LEVOFLOXACIN IV 5 mg/mL AUSTELL in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when LEVOFLOXACIN IV 5 mg/mL AUSTELL is given concomitantly with these medicines (see section 4.5).

Hepatobiliary disorders

Cases of hepatic necrosis up to fatal hepatic failure have been reported with levofloxacin as in LEVOFLOXACIN IV 5 mg/mL AUSTELL, primarily in patients with severe underlying diseases, e.g. sepsis (see section 4.8). Patients should be advised to stop treatment with LEVOFLOXACIN IV 5 mg/mL AUSTELL and contact their medical practitioner 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 while receiving LEVOFLOXACIN IV 5 mg/mL AUSTELL an eye doctor should be consulted immediately (see sections 4.7 and 4.8).

Superinfection

The use of levofloxacin as in LEVOFLOXACIN IV 5 mg/mL AUSTELL, especially if prolonged, may result in overgrowth of non-susceptible organisms. If superinfection occurs during treatment with LEVOFLOXACIN IV 5 mg/mL AUSTELL, appropriate measures should be taken.

Porphyria

Attacks of porphyria have occurred in patients with porphyria when taking fluoroquinolones such as levofloxacin as in LEVOFLOXACIN IV 5 mg/mL AUSTELL.

Sodium content

LEVOFLOXACIN IV 5 mg/mL AUSTELL contains 15,4 mmoL (354,2 mg) sodium per 100 mL dose. To be taken into consideration by patients on a controlled sodium diet (see section 2).

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on levofloxacin

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

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

Levofloxacin concentrations were about 13 % higher in the presence of fenbufen than when administered alone.

Probenecid and cimetidine

It has been reported that probenecid and cimetidine had a statistically significant effect on the elimination of levofloxacin as in LEVOFLOXACIN IV 5 mg/mL AUSTELL. The renal clearance of levofloxacin was reduced by cimetidine (24 %) and probenecid (34 %) due to blockade of 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 IV 5 mg/mL AUSTELL is co-administered with medicines that effect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

Angiotensin Converting Enzyme (ACE) Inhibitors / Angiotensin Receptor Blockers (ARBs)

Concomitant use of fluoroquinolones, such as levofloxacin as in LEVOFLOXACIN IV 5 mg/mL AUSTELL, with angiotensin converting enzyme (ACE) inhibitors / angiotensin receptor blockers (ARBs) may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3).

Other relevant information

Reported clinical pharmacology studies have shown that the pharmacokinetics of levofloxacin were not affected to any clinically relevant extent when levofloxacin as in LEVOFLOXACIN IV 5 mg/mL AUSTELL was administered together with the following medicines: calcium carbonate, digioxin, glibenclamide, ranitidine.

Effect of Levofloxacin on other medicines

Ciclosporin

It has been reported that the half-life of ciclosporin was increased by 33 % when co-administered with levofloxacin as in LEVOFLOXACIN IV 5 mg/mL AUSTELL.

Vitamin K antagonists

Increased coagulation tests (PT/INR) and / or bleeding, which may be severe, have been reported in patients treated with levofloxacin as in LEVOFLOXACIN IV 5 mg/mL AUSTELL in combination with a vitamin K antagonist (e.g. warfarin). Coagulation tests, therefore, should be monitored in patients on LEVOFLOXACIN IV 5 mg/mL AUSTELL treated with vitamin K antagonists (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 QT interval prolongation).

Other relevant information

In a pharmacokinetic interaction study, levofloxacin did not affect the pharmacokinetics of theophylline (which is a probe substrate for CYP1A2), indicating that LEVOFLOXACIN IV 5 mg/mL AUSTELL is not a CYP1A2 inhibitor.

Antidiabetic medicines

Disturbances of blood glucose, including hyperglycaemia and hypoglycaemia, have been reported in patients treated concomitantly with fluoroquinolones, such as levofloxacin as in LEVOFLOXACIN IV 5 mg/mL AUSTELL and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered (see section 4.4).

4.6 Fertility, pregnancy and lactation

Safety and efficacy of LEVOFLOXACIN IV 5 mg/mL AUSTELL in pregnant and breastfeeding women have not been established.

LEVOFLOXACIN IV 5 mg/mL AUSTELL should not be given to pregnant women or women who are

breastfeeding (see section 4.3).

Pregnancy

LEVOFLOXACIN IV 5 mg/mL AUSTELL is contraindicated in pregnancy. There is limited amount of data from the use of levofloxacin as in LEVOFLOXACIN IV 5 mg/mL AUSTELL 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 experimental data which suggests a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, LEVOFLOXACIN IV 5 mg/mL AUSTELL must not be used in pregnant women (see sections 4.3 and 5.3).

Breastfeeding

LEVOFLOXACIN IV 5 mg/mL AUSTELL is 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 experimental data which suggests a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, LEVOFLOXACIN IV 5 mg/mL AUSTELL must not be used in breastfeeding women (see sections 4.3 and 5.3).

Fertility

Levofloxacin as in LEVOFLOXACIN IV 5 mg/mL AUSTELL caused no impairment of fertility or reproductive performance in rats.

4.7 Effects on ability to drive and use machines

LEVOFLOXACIN IV 5 mg/mL AUSTELL may cause undesirable effects (e.g. dizziness/vertigo, drowsiness, visual disturbances) which 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). Patients should be advised not to drive and operate machines until they know how treatment with LEVOFLOXACIN IV 5 mg/mL AUSTELL affects them.

4.8 Undesirable effects

Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and post-market spontaneous reports with levofloxacin.

System Organ Class	Frequency		
	Frequent	**Less Frequent**	**Not known**
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 (may occur at first dose), anaphylactoid shock (may occur at first dose) (see section 4.4)

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, state of confusion, nervousness, psychotic reactions (with hallucination, paranoia), depression, agitation, abnormal dreams, nightmares	Psychotic with self-endangering, behaviour including suicidal ideation or suicide attempt (see section 4.4)
Nervous system disorders*	Headache, dizziness	Somnolence, tremor, dysgeusia, convulsions (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 dysrrhythmia and torsade de pointes (reported predominantly in patients with risk factors of QT prolongation), electrocardiogram QT prolonged (see sections 4.4 and 4.9), mitral and/or aortic valve regurgitation**
Vascular disorders	Phlebitis	Hypotension	
Respiratory, thoracic and		Dyspnoea	Bronchospasm, pneumonitis allergic

mediastinal disorders			
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 fatal cases with acute liver failure, primarily in patients with severe underlying diseases (see section 4.4), hepatitis
Skin and subcutaneous tissue disorders		Rash, pruritus, urticaria, hyperhidrosis	Toxic epidermal necrolysis, stevens-Johnson syndrome, erythema multiforme, photosensitivity reaction (see

(may occur even after the first dose)			section 4.4), leukocytoclastic vasculitis, stomatitis
Musculoskeletal and connective tissue disorders*		Arthralgia, myalgia, 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))	Rhabdomyolysis, tendon rupture (e.g. Achilles tendon) (see 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*	Infusion site reaction (pain, reddening)	Asthenia, pyrexia	Pain (including pain in back, chest, and extremities)

* Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendinitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies

associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see section 4.4).

** cases of mitral valve and /or 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 fluoroquinolones 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.

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

- attacks of porphyria in patients with porphyria.

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 toxicity studies in animals or clinical pharmacology studies performed with supra-therapeutic doses, the most important signs to be expected following acute overdose of levofloxacin as in LEVOFLOXACIN IV 5 mg/mL AUSTELL are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval as well as gastrointestinal reactions such as nausea and mucosal erosions.

CNS effects including state of confusion, convulsion, hallucination, and tremor have been observed in post marketing experience.

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body. No specific antidote exists.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 20.1.1 Broad and Medium Spectrum Antibiotics

Pharmacotherapeutic group: Quinolone antibacterials - Fluoroquinolones

ATC Code: J01MA12

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

Mechanism of action

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

PK / 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).

Mechanism 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 medicines.

Species for which acquired resistance may be a problem

Aerobic Gram-positive bacteria

Enterococcus faecalis

Staphylococcus aureus methicillin-resistant[#]

Coagulase negative *Staphylococcus spp*

Aerobic Gram-negative bacteria

Acinetobacter baumannii

Citrobacter freundii

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli

Klebsiella pneumoniae

Morganella morganii

Proteus mirabilis

Providencia stuartii

Pseudomonas aeruginosa

Serratia marcescens

Anaerobic bacteria

Bacteroides fragilis

Inherently Resistant Strains

Aerobic Gram-positive bacteria

Enterococcus faecium

[#] Methicillin-resistant *S. aureus* are very likely to possess co-resistance to fluoroquinolones, including levofloxacin.

5.2 Pharmacokinetic properties

The absolute bioavailability is 99 % to 100 %.

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 500mg doses, indicating widespread distribution into body tissues.

Penetration into tissues and body fluids:

Levofloxacin has been shown to penetrate into bronchial mucosa, epithelial lining fluid, alveolar macrophages, lung tissue, skin (blister fluid), prostatic tissue and urine. However, levofloxacin has poor penetration into cerebrospinal 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 intravenous administration of levofloxacin, it is eliminated relatively slowly from the plasma (t½: 6 – 8 h). 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/non-linearity

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

Special populations

Subjects with renal insufficiency

The pharmacokinetics of levofloxacin are affected by renal impairment. With decreasing renal function renal elimination and clearance are decreased, and elimination half-lives increased.

Elderly patients

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

Gender differences

Separate analysis for male and female subjects showed 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 foetuses 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 (CHL) 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 mouse 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 tumour development in a photocarcinogenicity assay.

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

Sodium chloride

Hydrochloric acid 10 % (for pH adjustment)

Sodium Hydroxide 0,1N (for pH adjustment)

Water for Injection

6.2 Incompatibilities

LEVOFLOXACIN IV 5 mg/mL AUSTELL must not be mixed with heparin or alkaline solutions (e.g. sodium hydrogen carbonate).

LEVOFLOXACIN IV 5 mg/mL AUSTELL must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial: 36 months.

In use: From a microbiological point of view, the product should be used immediately. If not used immediately (within 3 hours), in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Chemical and physical in use stability has been demonstrated for 72 hours at 25 °C in 0,9 % sodium chloride solution, 5 % dextrose solution and 5 % dextrose in lactated Ringer's solution, and 24 hours at 2 to 8 °C in combined solutions for parenteral nutrition.

6.4 Special precautions for storage

Do not store above 25 °C.

Keep the vials in the outer carton, in order to protect from light.

For storage conditions of the diluted product see section 6.3.

6.5 Nature and contents of container

100 ml solution in a vial (Type I, glass) with either chlorobutyl or bromobutyl rubber stopper and blue, polypropylene flip-off cap.

Pack size: 1 vial per box or 12 vials per box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This product is for single use only.

LEVOFLOXACIN IV 5 mg / mL AUSTELL solution for infusion should be used immediately after perforation of the rubber stopper in order to prevent any bacterial contamination.

No protection from light is necessary during infusion.

Any unused product or waste material should be disposed of in accordance with local requirements.

LEVOFLOXACIN IV 5 mg/mL AUSTELL is compatible with the following infusion solutions:

- 0,9 % sodium chloride solution USP (Isotonic saline solution)
- 5,0 % dextrose injection, USP
- 2,5 % dextrose in Ringer solution
- Combination solutions for parenteral nutrition (amino acids, carbohydrates, electrolytes).

See 6.2 for incompatibilities.

The solution should be visually inspected prior to use. It must only be used if the solution is clear, greenish-yellow solution, practically free from particles.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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10. DATE OF REVISION OF THE TEXT