1.5.5.2 CLEAN AMENDED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

LEVOFLOXACIN TRINITY 250 (Film coated tablets)

LEVOFLOXACIN TRINITY 500 (Film coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

LEVOFLOXACIN TRINITY 250: Each film coated tablet contains levofloxacin hemihydrate equivalent to levofloxacin 250 mg.

LEVOFLOXACIN TRINITY 500: Each film coated tablet contains levofloxacin hemihydrate equivalent to levofloxacin 500 mg.

Sugar free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film coated tablets.

LEVOFLOXACIN TRINITY 250: Light Pink coloured capsule shaped, film coated tablets debossed with break line on both sides, separating “2” & “50” on one side and “10” & “82” on other side.

LEVOFLOXACIN TRINITY 500: Brick red coloured capsule shaped, film coated tablets debossed with break line on both sides, separating “8” & “3” on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- Acute exacerbations of chronic bronchitis: caused by *H. influenzae, K. pneumoniae, M. catarrhalis, H. parainfluenzae* or *S. pneumoniae.*
- Pneumonia (community acquired): caused by *H. influenzae, S. pneumoniae, M.catarrhalis, H. parainfluenzae, K. pneumonia, 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 *K. pneumoniae, S. faecalis, P. mirabilis,* and *P. aeruginosa.*
- Uncomplicated urinary tract infections in women: caused by *K. pneumoniae.*
- Skin and soft tissue infections (uncomplicated): caused by *S. pyogenes, Acinetobacter calcoaceticus, P. mirabilis, K. pneumoniae* or *S. faaecalis*.
- Skin and soft tissue infections (complicated): caused by *S. pyogenes, P. mirabilis, K. pneumoniae, S. faecalis, K. oxytoca.*
- Intra-abdominal infections: caused by anaerobic micro-organisms.

4.2 Posology and method of administration

Posology

LEVOFLOXACIN TRINITY tablets: **LEVOFLOXACIN TRINITY** tablets should be swallowed whole, without crushing. **LEVOFLOXACIN TRINITY** tablets may be taken on an empty stomach or with meals. **LEVOFLOXACIN TRINITY** 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 **LEVOFLOXACIN TRINITY** should be continued for a minimum of

48 to 72 hours after it has become evident that the patient has a bacterial infection. The duration of therapy varies according to the course of the disease.

The following daily dose are recommended for **LEVOFLOXACIN TRINITY**:

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

Special populations

Renal impairment;

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:

  - 250 or 500 mg once daily: a normal single dose should be given initially and then reduced by half this dose once daily.
  - 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:
  - 250 mg once daily: a normal single dose should be given initially and then reduced to 125 mg every 48 hours.
  - 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.
  - 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.
  - 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.
  - 500 mg twice daily: should be given 500 mg initially and then this dose should be reduced to 125 mg every 24 hours.

Elderly population:

No adjustment of dosage is required in the elderly in patients.

Hepatic impairment:

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

Method of administration

For oral administration.

4.3 Contraindications

The use of **LEVOFLOXACIN TRINITY** is contraindicated in:

- Previous hypersensitivity reaction to levofloxacin, other quinolones, or to any of the ingredients of **LEVOFLOXACIN TRINITY** listed in section 6.1.
- Epilepsy.
- Patients with history of tendon disorders associated with previous fluoroquinolone administration.
- Children or adolescents (under 18 years of age).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Caution should be exercised when using **LEVOFLOXACIN TRINITY** in patients:

- prone to seizures, such as patients with pre-existing central nervous system lesions,
- being treated with nonsteroidal anti-inflammatory medicines or using medicines which lower the cerebral seizure threshold, such as theophylline,
- being tested for tuberculosis as **LEVOFLOXACIN TRINITY** inhibit the growth of *Mycobacterium tuberculosis* and therefore may give false-negative results in the bacteriological diagnosis of tuberculosis,
- exposed to ultraviolet (UVA) from sun beds, in order to prevent photosensitisation,
- with diabetes mellitus, as hypoglycaemia may occur.

Fluoroquinolones, such as **LEVOFLOXACIN TRINITY**, have been known to trigger porphyria attacks.

Suspicion of pseudomembranous colitis requires immediate cessation of treatment with appropriate specific antibiotic therapy.

Psychotic reactions have been reported to occur already after the first dose. In the event of psychotic side-effects, **LEVOFLOXACIN TRINITY** must be discontinued immediately and the doctor informed. **LEVOFLOXACIN TRINITY** should be used with caution in patients who are psychotic or have a history of psychotic illness.

In the event of allergic manifestations, **LEVOFLOXACIN TRINITY** must be discontinued immediately. Medical treatment (therapy for shock) is imperative.

If tendonitis is suspected, treatment with **LEVOFLOXACIN TRINITY** must be discontinued immediately and appropriate treatment (e.g., immobilisation) must be initiated for the affected tendon. The risk of tendon rupture is higher in the elderly and in patients on corticosteroids. Tendon rupture may occur within 48 hours after starting treatment with **LEVOFLOXACIN TRINITY** and may be bilateral. It may still occur weeks after stopping treatment with **LEVOFLOXACIN TRINITY**.

Patients with glucose-6-phosphate dehydrogenase deficiency may be prone to haemolytic reactions when treated with quinolone antibacterial agents. Therefore, if **LEVOFLOXACIN TRINITY** has to be used in these patients, patients should be monitored for potential occurrence of haemolysis.

For patients with known risk factors for prolongation of the QT interval such as, for example:

- congenital long QT syndrome
- concomitant use of medicines that are known to prolong the QT interval (e.g., Class IA and III antidysrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

- uncorrected electrolyte imbalance (e.g., hypokalaemia, hypomagnesaemia)
- cardiac disease (e.g., heart failure, myocardial infarction, bradycardia)

Caution should be exercised when taking **LEVOFLOXACIN TRINITY**. In addition, elderly patients and women may be more sensitive to QTc-prolonging medicines. Therefore, caution should be taken when using fluoroquinolones, including **LEVOFLOXACIN TRINITY**, in these populations.

LEVOFLOXACIN TRINITY may have neuromuscular blocking activity and may therefore exacerbate muscle weakness in patients with myasthenia gravis. **LEVOFLOXACIN TRINITY** is not recommended in patients with a known history of myasthenia gravis as postmarketing serious adverse reactions, including deaths and the requirement for respiratory support, have been associated with fluoroquinolone use in patients with myasthenia gravis.

Methicillin-resistant *S. aureus* are likely to possess co-resistance to fluoroquinolones, including levofloxacin. Therefore, for the treatment of known or suspected MRSA infections, **LEVOFLOXACIN TRINITY** is not recommended. **LEVOFLOXACIN TRINITY** can be considered if the laboratory results have confirmed susceptibility of the organism to levofloxacin and commonly recommended antibacterial agents for the treatment of MRSA-infections are considered inappropriate.

4.5 Interaction with other medicines and other forms of interaction

The absorption of **LEVOFLOXACIN TRINITY** 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 **LEVOFLOXACIN TRINITY** tablet administration.

LEVOFLOXACIN TRINITY is known to inhibit metabolism of some medicines and may interfere with the clearance of medicines, such as theophylline, or non–steroidal anti-inflammatory medicines that lower the seizure threshold.

LEVOFLOXACIN TRINITY may increase plasma warfarin levels. Close monitoring of INR is therefore required.

LEVOFLOXACIN TRINITY may disturb blood glucose levels, both hypoglycaemia and hyperglycaemia have been reported in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g., glibenclamide) or with insulin. Careful monitoring of blood glucose is recommended.

4.6 Fertility, pregnancy and lactation

The use of **LEVOFLOXACIN TRINITY** during pregnancy and lactation is contra-indicated (see section 4.3). Animal studies have shown that joint development in growing organisms has been adversely affected.

4.7 Effects on ability to drive and use machines

On the basis of the reported adverse reactions, such as dizziness, visual and auditory disturbances and muscular incoordination **LEVOFLOXACIN TRINITY** may have a minor or moderate influence on driving or operating machinery, therefore caution is advised.

4.8 Undesirable effects

a. Summary of the safety profile

Not applicable

b. Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Less Frequent	Fungal overgrowth, proliferation of other resistant organisms
Blood and lymphatic system disorders	Less Frequent	Eosinophilia, leukopenia, neutropenia, thrombocytopenia, agranulocytosis
	Frequency unknown	Haemolytic anaemia, pancytopenia
Immune system disorders	Less Frequent	Pruritus, rash, urticaria, vasculitis, angio-edema, hypotension, anaphylactic-like shock, allergic pneumonitis
	Frequency unknown	Severe bullous eruptions such as Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, hypersensitivity vasculitis
Metabolism and nutrition disorders	Less Frequent	Hypoglycaemia (especially in patients with diabetes mellitus)
Psychiatric disorders	Less Frequent	Anxiety, depression, psychotic reactions, agitation, confusion, hallucinations
Nervous system disorders	Frequent	Tremor, disturbances of taste and smell
	Less Frequent	Headache, dizziness, restlessness, drowsiness, insomnia, paraesthesia, convulsions, visual and auditory disturbances
Gastrointestinal disorders	Frequent	Nausea, diarrhoea, abdominal or stomach pain or discomfort, loss of appetite, vomiting

	Less Frequent	Bloody diarrhoea, which in some cases may be indicative of pseudomembranous colitis
Hepatobiliary disorders	Less Frequent	Increase in liver enzymes, increase in bilirubin, hepatitis, jaundice
Skin and subcutaneous tissue disorders	Less Frequent	Photosensitivity reactions, rash
Musculoskeletal and connective tissue disorders	Less Frequent	Arthralgia, myalgia, tendon disorders e.g., tendonitis of the Achilles tendon, tendon rupture, muscle weakness (especially relevant in patients with myasthenia gravis)
	Frequency unknown	Rhabdomyolysis
Renal and urinary disorders	Less Frequent	Interstitial nephritis, crystalluria, acute renal failure
General disorders and administration site conditions	Less Frequent	Asthenia, fever
	Frequency unknown	Local pain
Investigations	Frequency unknown	Increase in serum creatinine

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

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

4.9 Overdose

The symptoms that can be expected from an acute overdosage of **LEVOFLOXACIN TRINITY** 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.

LEVOFLOXACIN TRINITY is not effectively removed by haemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.20.1 Broad and Medium Spectrum Antibiotics.

Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones, ATC code: J01MA12.

Levofloxacin is a broad-spectrum bactericidal agent from the chemical group fluoroquinolone. Levofloxacin is the pure(-) – (S) – enatiomer 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 fluoroquinolones *in vitro.* The antibacterial spectrum of levofloxacin covers many Gram-positive and Gram-negative bacteria.

Organisms for which acquired resistance may be a problem

Aerobic Gram-positive bacteria

Enterococcus faecalis, methicillin-resistant *staphylococcus aureus* (Methicillin-resistant *S. aureus* are very likely to possess co-resistance to fluoroquinolones, including levofloxacin.), coagulase negative *Staphylococcus spp*.

Aerobic Gram- negative bacteria

Acinetobacter baumannii, Citrobacter freundii, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Klebsiella pneumonia, Morganella morganii, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, Serratia marcescens

Anaerobic bacteria

Bacteroides fragilis

Inherently Resistant Strains

Aerobic Gram-positive bacteria: *Enterococcus faecium*

5.2 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:

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

Distribution in tissues and fluids: Levofloxacin penetrates well into lung tissue, bone tissue, bronchial mucosa, epithelial lining fluid and blister fluid.

Biotransformation:

Levofloxacin is metabolised to a small degree to inactive metabolites being desmethyl levofloxacin and levofloxacin-N-oxide.

Elimination:

Levofloxacin is excreted largely unchanged primarily via the kidney. The elimination half-life of levofloxacin is six to eight hours after oral and intravenous administration.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone XL 10

Ferric oxide red (C.I No. 77491)

Ferric oxide yellow (C.I No. 77491)

Hypromellose (3 cps)

Hypromellose 2190 (6 cps)

Magnesium stearate

Microcrystalline cellulose

Polyethylene glycol 400

Polysorbate-80

Titanium dioxide (C.I No. 77891)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

100’s: Printed unit carton containing 10 blister packs (composed of clear transparent PVC film sealed with Aluminum foil) of 10 tablets each.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

TRINITY PHARMA (PTY) LTD

381 Rossouw Street

Murrayfield

Pretoria

South Africa

8 REGISTRATION NUMBER(S)

LEVOFLOXACIN TRINITY 250: 44/20.1.1/0421.

LEVOFLOXACIN TRINITY 500: 44/20.1.1/0422.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 December 2013.

10 DATE OF REVISION OF THE TEXT

09 November 2022.