**PROFESSIONAL INFORMATION FOR**

**TAVALOXX 250 / 500 / 750 TABLETS**

## SCHEDULING STATUS

S4

## 1. NAME OF THE MEDICINE

**TAVALOXX 250**, levofloxacin 250 mg, Tablets

**TAVALOXX 500**, levofloxacin 500 mg, Tablets

**TAVALOXX 750**, levofloxacin 750 mg, Tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TAVALOXX 250

Each tablet contains levofloxacin hemihydrate equivalent to 250 mg levofloxacin.

TAVALOXX 500

Each tablet contains levofloxacin hemihydrate equivalent to 500 mg levofloxacin.

TAVALOXX 750

Each tablet contains levofloxacin hemihydrate equivalent to 750 mg levofloxacin.

Sugar free.

For the full list of excipients, see **section 6.1**.

## 3. PHARMACEUTICAL FORM

Tablets

TAVALOXX 250: Brownish pink, film-coated oval, biconvex tablets, debossed ‘250’ on one side and plain on the other side.

TAVALOXX 500: Pale yellow, film-coated oval, biconvex tablets, debossed ‘500’ on one side and plain on the other side.

TAVALOXX 750: White, film-coated, oval, biconvex tablets, debossed ‘750’ on one side and plain on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

TAVALOXX is indicated in adults 18 years and older, in the treatment of the following bacterial infections:

- **Acute exacerbations of chronic bronchitis:** caused by *H. influenzae, K. pneumoniae, S. aureus, M. catarrhalis, E. coli, H. parainfluenzae or S. pneumoniae*.
- **Pneumonia (community-acquired):** caused by *H. influenzae, S. pneumoniae, S. aureus, M. catarrhalis, H. parainfluenzae, K. pneumoniae, E. coli, Mycoplasma pneumoniae, Chlamydia pneumoniae or Legionella pneumophila.*
- **Sinusitis:** caused by *H. influenzae, S. pneumoniae, S. aureus, M. catarrhalis or H. parainfluenzae.*
- **Urinary tract infections (complicated) and acute pyelonephritis:** caused by *E. coli, K. pneumoniae, S. faecalis, P. mirabilis, Enterobacter cloacae and P. aeruginosa*.
- **Uncomplicated urinary tract infections in women:** caused by *E. coli, K. pneumoniae.*

- **Skin and soft tissue infections (uncomplicated):** caused by *S. aureus, S. pyogenes, Acinetobacter calcoaceticus, E. cloacae, P. mirabilis, P. aeruginosa, E. coli, K. pneumoniae or S. faecalis.*
- **Skin and soft tissue infections (complicated):** caused by *S. aureus, S. pyogenes, P. mirabilis, E. coli, K. pneumoniae, S. faecalis, E. cloacae, K. oxytoca*.
- I**ntra-abdominal infections:** caused by *E. coli* and anaerobic micro-organisms.

TAVALOXX 750~~:~~ is indicated for hospital acquired pneumonia: due to *H. influenzae, S. pneumoniae and methicillin-sensitive S. aureus.*

## 4.2 Posology and method of administration

**Posology**

TAVALOXX is to be taken once or twice daily.

The dosage will depend on the type of pathogen and the severity of the infection. The use of TAVALOXX 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 is recommended for TAVALOXX:

**Daily dosage recommended in patients with normal renal function**

*Bronchitis, bacterial exacerbations:* 500 mg once daily for 5 to 10 days. Alternatively, 750 mg once daily for 3 to 5 days if caused by *H. influenzae*, methicillin-sensitive *S. aureus*, *M. catarrhalis*, *H. parainfluenzae* or *S. pneumoniae*.

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

Alternatively, 750 mg once daily for 5 days if caused by *H. influenzae, S. pneumoniae, H. parainfluenzae, M. pneumoniae, C. pneumoniae* or *L. pneumophila*.

*Sinusitis:* 500 mg once daily for 10 to 14 days. Alternatively, 750 mg once daily for 5 days.

*Urinary tract infections (complicated) and acute pyelonephritis:* 250 mg once daily for 10 days.

*Urinary tract infections (uncomplicated) in women:* 250 mg once daily for 3 days.

*Uncomplicated skin and soft tissue infections:* 250 to 500 mg once daily for 7 to 10 days.

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

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

*Above infections when bacteraemia or septicaemia is present:* 500 mg twice daily for 10 to 14 days.

*Hospital acquired pneumonia:* 750 mg once daily for 10 to 14 days if caused by *H. influenzae, S. pneumoniae* and methicillin-sensitive *H. influenzae, S. pneumoniae* and methicillin-sensitive *S. aureus.*

**Special populations**

**Elderly population**

No adjustment of dosage is required in the elderly.

**Daily dosage recommended in patients with impaired renal function**

Caution is advised when prescribing fluoroquinolones such as TAVALOXX for patients with renal impairment as the risk of fluoroquinolone-induced tendinitis and tendon rupture may be exacerbated in these patients.

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.

In patients meant to be taking 750 mg once daily: a normal single dose should be given initially, and then 750 mg should be administered every 48 hours.

*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.

In patients meant to be taking 750 mg once daily: a normal single dose should be given initially, and then reduced to 500 mg administered every 48 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.

In patients meant to be taking 750 mg once daily: a normal single dose should be given initially, and then reduced to 500 mg administered every 48 hours.

**Hepatic impairment**

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

**Paediatric population**

Levofloxacin is contraindicated in children and adolescents (under 18 years of age) (see **section 4.3**).

**Method of administration**

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

## 4.3 Contraindications

TAVALOXX is contraindicated in:

- Patients with known hypersensitivity to levofloxacin, other quinolones, or to any of the excipients in TAVALOXX (see **section 6.1**).

- Epilepsy.
- Patients with history of tendon disorders associated with fluoroquinolone administration.
- Children or adolescents (under 18 years of age).
- Pregnancy and lactation.
- Patients with moderate to severe renal impairment who are using ACE inhibitors or renin-angiotensin blockers concomitantly.
- 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.

## 4.4 Special warnings and precautions for use

Caution should be exercised when using TAVALOXX in patients:

- prone to seizures, such as patients with pre-existing central nervous system lesions,
- being treated with fenbufen or non-steroidal anti-inflammatory medicines,
- using medicines which lower the cerebral seizure threshold, such as theophylline,
- driving or operating machinery, as the use of TAVALOXX may alter the ability to drive or to operate machinery,
- being tested for tuberculosis as TAVALOXX inhibit the growth of *Mycobacterium tuberculosis* and therefore may give false-negative results in the bacteriological diagnosis of tuberculosis,
- exposed to ultraviolet light such as sunlight through window glass or longer wavelength ultraviolet (UVA) from sunbeds, in order to prevent photosensitisation.

For the indication listed below, TAVALOXX should only be prescribed where other antimicrobials are considered not to be an appropriate treatment option, have failed, are contraindicated, or not tolerated:

- Treatment of mild to moderate infections including acute exacerbation of chronic

bronchitis.

Disturbances in blood glucose, including both hyperglycaemia and hypoglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic medicine or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see **section 4.8**).

**Pseudomembranous colitis**

Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with TAVALOXX, may be symptomatic of pseudomembranous colitis due to *Clostridium difficule.* If pseudomembranous colitis is suspected, TAVALOXX must be stopped immediately (see **section 4.8**).

**Tendinitis**

Tendinitis, which is observed with the use of quinolones, such as TAVALOXX, may occasionally lead to tendon rupture involving the Achilles tendon in particular. This effect may occur within 48 hours of starting treatment and may be bilateral. Elderly patients are more prone to tendinitis. Tendinitis and tendon rupture may be exacerbated in patients with renal impairment and with patients with solid organ transplants. The risk of tendon rupture may be increased by co-administration of corticosteroids. If tendinitis is suspected, treatment with TAVALOXX must be stopped immediately. Tendinitis / rupture may occur after several weeks after discontinuation of TAVALOXX (see **section 4.8**).

**Prolonged, disabling and potentially irreversible serious adverse drug reactions**

Very rare cases of prolonged (continuing for 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. TAVALOXX should be discontinued immediately at the first signs or symptoms of any serious adverse reaction, such as tendinitis and tendon rupture, muscles pain, muscle weakness, joint swelling, peripheral neuropathy and central nervous system effects and patients should be advised to contact their health care for advice.

**Elderly population**

Caution is advised when prescribing for the elderly, especially patients with renal impairment, patients with solid organ transplants, and those concurrently treated with corticosteroids, as the risk of fluoroquinolone-induced tendinitis and tendon rupture may be exacerbated in these patients.

**Patients with renal impairment**

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

Concomitant use of fluoroquinolones, such as TAVALOXX and ACE inhibitors / renin-angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see **section 4.3** and **4.8**). Renal function should be assessed before initiating treatment, with fluoroquinolones or ACE inhibitors / renin-angiotensin receptor blockers.

**QT-interval prolongation**

Caution should be when using fluoroquinolones, including TAVALOXX, in patients with known risk factors for prolongation of the QT-interval such as:

- the elderly

- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- congenital long QT syndrome
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
- 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**).

Women and the elderly may be more sensitive to QTc-prolonging medicines. Therefore, caution should be taken when fluoroquinolones, including TAVALOXX, are administered in these populations.

**Vascular disorders**

There is some evidence of an association of fluroquinolone use in the risk of aortic aneurysm and dissection particularly in the elderly population. Fluroquinolones should be prescribed after careful benefit-risk assessment and after consideration of other therapeutic option to patients at risk for aortic aneurysm and dissection. The conditions predisposing to aortic aneurysm and dissection include a family history of aneurysm disease, pre-existing aortic aneurysm or aortic dissection Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, and atherosclerosis.

In case of sudden severe abdominal pain, chest pain or back pain patients should be advised to immediately consult a doctor in an emergency department (see **section 4.8**).

Fluoroquinolones, such as TAVALOXX, should only be prescribed to patients with a pre-existing dilated aorta, aortic aneurysm or dissection or the presence of other risk factors predisposing to aortic aneurysm/dissection, where other antimicrobials have been considered not to be an appropriate treatment option have failed, are contraindicated, or cannot be tolerated.

**Cardiac disorders**

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

**Glucose-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 quinolones, such as TAVALOXX. The potential occurrence of haemolysis should be monitored.

**Peripheral neuropathy**

Sensory or sensorimotor peripheral neuropathy has been reported in patients receiving fluoroquinolones, including TAVALOXX, which can be rapid in its onset. TAVALOXX should be discontinued if the patient experiences symptoms of neuropathy. This would minimise the possible risk of developing an irreversible condition (see **section 4.8**).

In patients treated with TAVALOXX, determination of opiates in urine may give a false-positive result.

Methicillin resistant *S.aureus* (MRSA) are very likely to possess co-resistance to fluoroquinolones, including levofloxacin. Levofloxacin 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 agents for the treatment of MRSA-infections are not considered appropriate.

Resistance to fluoroquinolones of *E.coli* – the most common pathogen involved in urinary tract infections – varies. Prescribers are advised to consider the local prevalence of resistance in *E. coli* to fluoroquinolones.

**Hypersensitivity reactions**

Levofloxacin may cause serious, potentially fatal hypersensitivity reactions (e.g. angio-oedema up to anaphylactic shock), occasionally following the initial dose. Patients should discontinue treatment immediately and contact their doctor who will initiate appropriate emergency measures (see **section 4.8**).

**Severe bullous reactions**

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

**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 a single dose of levofloxacin. Levofloxacin should then be discontinued and appropriate measures instituted. Caution is therefore recommended if levofloxacin is indicated in psychotic patients or in patients with a history of psychiatric disease (see **section 4.8**).

**Hepatobiliary disorders**

Hepatic necrosis up to fatal hepatic failure has been reported with levofloxacin, primarily in patients with severe underlying diseases, e.g. sepsis. Treatment should be stopped, and patients

should contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

**Exacerbation of myasthenia gravis**

Fluoroquinolones, such as levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. TAVALOXX is not recommended in patients with a known history of myasthenia gravis as post marketing serious adverse reactions, including deaths and the requirement for respiratory support, have been associated with fluoroquinolone use in patients with myasthenia gravis.

**Vision disorders**

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

**Superinfection**

The use of levofloxacin, as in TAVALOXX, especially if prolonged, may result in overgrowth of non-susceptible organisms. if superinfection occurs during therapy, appropriate measures should be taken.

**Paediatric population**

**TAVALOXX SHOULD NOT BE GIVEN TO PATIENTS UNDER 18 YEARS OF AGE (see section 4.3).**

## 4.5 Interaction with other medicines and other forms of interaction

The absorption of TAVALOXX 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 TAVALOXX tablet administration.

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

Concomitant use of fluoroquinolones, such as TAVALOXX and ACE inhibitors / renin-angiotensin receptor blockers may precipitate acute kidney injury (see **section 4.3**). Careful consideration should be given to age, renal function, hydration status and concomitant prescribing of diuretics or NSAIDs, and to monitoring of changes in renal function throughout treatment.

Caution should be exercised when TAVALOXX is co-administered with medicines that affect the tubular renal secretion such as probenecid and cimetidine, especially in renal impaired patients.

Increased coagulation tests (PT / INR) and/or bleeding which may be severe, have been reported in patients treated with TAVALOXX in combination with a vitamin K antagonist (e.g. warfarin). Coagulation tests should be monitored in patients treated with vitamin K antagonists.

TAVALOXX should be used with caution in patients receiving medicines known to prolong the QT interval [e.g. Class IA and III antidysrhythmics, tricyclic antidepressants, macrolides] (see **section 4.4**).

## 4.6 Fertility, pregnancy and lactation

### Pregnancy

The use of TAVALOXX during pregnancy is contraindicated (see **section 4.3**).

**Breastfeeding**

The use of TAVALOXX during lactation is contraindicated (see **section 4.3**).

## 4.7 Effects on ability to drive and use machines

TAVALOXX may alter reactivity to such an extent that the ability to drive or to operate machinery may be impaired.

## 4.8 Undesirable effects

The following side effects have been reported:

| MedDRA system organ class | Frequency | Side effects |
|---|---|---|
| **Infections and infestations** | *Less frequent* | Fungal infection, pathogen resistance, fungal overgrowth and proliferation of other resistant micro-organisms. |
| **Blood and the lymphatic system disorders** | *Less frequent* | Leukopenia, eosinophilia, neutropenia, thrombocytopenia |
| | *Frequency unknown* | Pancytopenia, agranulocytosis, haemolytic anaemia. |
| **Immune system disorders** | *Less frequent* | Angio-oedema, allergic manifestations, allergic pneumonitis, hypersensitivity, pruritus, rash, urticaria, vasculitis reactions. |
| | *Frequency unknown* | Anaphylactic shock, anaphylactoid shock. severe bullous eruptions such as Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme, hypersensitivity vasculitis. |
| **Metabolism and nutrition disorders** | *Less frequent* | Hypoglycaemia, particularly in diabetic patients (see **section 4.4**), anorexia. |
| | *Frequency unknown* | Hyperglycaemia, hypoglycaemic coma. |
| **Psychiatric disorders** | *Frequent* | Insomnia. |
| | *Less frequent* | Anxiety, confusional state, psychotic disorder (with e.g. hallucination) depression, agitation, nervousness, abnormal dreams, nightmares. |
| | *Frequency unknown* | Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt. |
| **Nervous system disorders** | *Frequent* | Headache, dizziness. |
| | *Less frequent* | Somnolence, tremor, dysgeusia, paraesthesia, convulsion. |

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| | *Frequency unknown* | Peripheral sensory neuropathy, peripheral sensory motor neuropathy, parosmia including anosmia, dyskinesia, extrapyramidal disorder, ageusia, syncope, benign intracranial hypertension.<br>In the event of such adverse reactions, TAVALOXX must be discontinued immediately and the medical practitioner informed. |
| **Eye disorders** | *Less frequent* | Visual disturbances (such as blurred vision). |
| | *Frequency unknown* | Transient vision loss, uveitis. |
| **Ear and labyrinth disorders** | *Less frequent* | Vertigo, tinnitus. |
| | *Frequency unknown* | Hearing impaired, hearing loss. |
| **Cardiac disorders** | *Less frequent* | Tachycardia, palpitation. |
| | *Frequency unknown* | Ventricular tachycardia, which may result in cardiac arrest, ventricular arrhythmia and torsades de pointes (predominantly in patients with risk factors for QT prolongation, electrocardiogram QT prolonged. |
| **Vascular disorders** | *Less frequent* | Hypotension. |
| **Respiratory, thoracic and mediastinal disorders** | *Less frequent* | Dyspnoea, allergic pneumonitis. |
| | *Frequency unknown* | Bronchospasm. |
| | *Less frequent* | Nausea, diarrhoea, vomiting. |

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| **Gastrointestinal disorders** | *Frequency unknown* | Gastrointestinal symptoms may occur (gastric or abdominal symptoms, loss of appetite, abdominal pain, dyspepsia, flatulence, constipation). The onset of diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with TAVALOXX, may indicate the appearance of pseudomembranous colitis. Suspicion of pseudomembranous colitis requires immediate cessation of treatment with appropriate specific antibiotic therapy. |
| **Hepatobiliary disorders** | *Frequent* | Hepatic enzyme increased (ALT / AST, alkaline phosphatase, GGT). |
| | *Less frequent* | Blood bilirubin increased. |
| | *Frequency unknown* | Jaundice and sever liver injury, including cases with fatal acute liver failure, primarily in patients with severe underlying diseases. |
| **Skin and subcutaneous tissue disorders** | *Less frequent* | Rash, pruritus, urticaria, hyperhidrosis. |
| | *Frequency unknown* | Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, photosensitivity reaction, leukocytoclastic vasculitis, stomatitis. |
| **Musculoskeletal, connective tissue and bone disorders** | *Less frequent* | Arthralgia, myalgia, tendon disorder including tendinitis (e.g. Achilles tendon), muscular weakness which may be of special importance in patients with myasthenia gravis. |
| | *Frequency unknown* | Rhabdomyolysis, tendon rupture (e.g. Achilles tendon, ligament rupture, muscle rupture, arthritis. |
| **Renal and urinary disorders** | *Less Frequent:* | Blood creatinine increased; renal failure acute (e.g. due to interstitial nephritis. |

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|---|---|---|
| ***General disorders and administrative site conditions*** | *Less frequent* | Asthenia, pyrexia (fever), disturbances of taste and smell, fungal overgrowth and proliferation of other resistant micro-organisms. |
| | *Frequency unknown* | Pain (including pain in back, chest and extremities). |

**Post-marketing**

| **MedDRA system organ class** | **Frequency** | **Side effects** |
|---|---|---|
| **Metabolism and nutrition disorders** | *Frequency unknown* | Hyperglycaemia, hypoglycaemic coma (see-**section 4.4**). |
| **Cardiac disorders** | *Frequency unknown* | Cases of mitral valve and/or aortic valve regurgitation were reported in patients treated with oral fluoroquinolones, such as TAVALOXX. 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 and/or aortic regurgitation cases was diagnosed. |

**Description of selected adverse reactions**

TAVALOXX is known to possibly trigger attacks of porphyria in patients suffering from 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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website,

or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

### 4.9 Overdose

According to studies in animals, the most important signs to be expected following acute overdosage of TAVALOXX 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. The treatment of an overdosage is only symptomatic and supportive.

TAVALOXX is not effectively removed by haemodialysis or peritoneal dialysis.

In the event of overdose the patient should be carefully observed (including ECG monitoring) and symptomatic treatment should be implemented. In case of acute oral overdosage, gastric lavage should also be considered, and antacids may be used for protection of gastric mucosa.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacological classification: A 20.1.1 - 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) – enantiomer of ofloxacin.

***Mechanism of action***

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

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

The antibacterial spectrum of levofloxacin covers many Gram-positive and Gram-negative bacteria. Levofloxacin can be used successfully against the following organisms:

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

**Gram-positive organisms:** *Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes* and *Streptococcus faecalis.*

**Other organisms:** *Chlamydia pneumoniae, Legionella pneumophila* and *Mycoplasma pneumoniae.*

## 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 %.

The absorption of levofloxacin is significantly reduced when administered with iron salts, antacids and sucralfate.

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

conditions are reached after approximately 48 hours following levofloxacin 750 mg once daily dosage. Multiple doses of 750 mg once daily shows negligible accumulation.

***Distribution***

Levofloxacin is approximately 30 to 40 % 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.

***Biotransformation***

Levofloxacin is metabolised to a small degree to inactive metabolites being desmethyllevofloxacin 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.

***Excretion***

The elimination half-life of levofloxacin is six to eight hours after oral and intravenous administration. Levofloxacin is excreted largely unchanged, primarily via the kidney The mean apparent total body clearance of levofloxacin following a 500 mg single dose is 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.

***Distribution in tissues and fluids***

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

**Tablet core**:

Croscarmellose sodium

Magnesium stearate

Microcrystalline cellulose

Povidone

Starch.

**Coating**

TAVALOXX 250: Opadry Pink (Hypromellose, titanium dioxide, macrogol and iron oxide red).

TAVALOXX 500: Opadry Yellow (Hypromellose, titanium dioxide, macrogol and iron oxide red).

TAVALOXX 750: Opadry White (Hypromellose, titanium dioxide and macrogol).

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

24 months

### 6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Keep the blisters in the outer carton until required for use.

### 6.5 Nature and contents of container

TAVALOXX 250: TAVALOXX 250 is packed in a carton containing transparent PVC/PVDC and aluminium foil blister strips of 3, 5 or 10 tablets.

TAVALOXX 500: TAVALOXX 500 is packed in a carton containing transparent PVC/PE/PVDC and aluminium foil blister strips of 5 or 10 tablets.

TAVALOXX 750: TAVALOXX 750 is packed in a carton containing transparent PVC/PVDC and aluminium foil blister strips of 5 or 10 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

**CIPLA MEDPRO (PTY) LTD.**

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

## 8. REGISTRATION NUMBER(S)

TAVALOXX 250: 41/20.1.1/0007

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|---|
| Botswana: S2 BOT0801440 |
| Namibia: NS2 09/20.1.1/0026 |

TAVALOXX 500: 41/20.1.1/0008

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| Botswana: S2 BOT0801421 |
| Namibia: NS2 09/20.1.1/0025 |

TAVALOXX 750: 41/20.1.1/0009.

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| Namibia: NS2 09/20.1.1/0024 |

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 05 October 2007.

Latest renewal: Not applicable.

## 10. DATE OF REVISION OF THE TEXT

02 December 2025