Professional Information for ZYBACT 250 mg & 500 mg

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ZYBACT 250 mg film-coated tablets

ZYBACT 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Sugar free.

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

ZYBACT 250 mg: Pink coloured, capsule-shaped, biconvex, film-coated tablet with a break-line on both sides, with a thickness of approximately 4,30 mm.

ZYBACT 500 mg: Pink coloured, capsule-shaped, biconvex, film-coated tablet with a break-line on both sides, with a thickness of approximately 5,50 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZYBACT is indicated for use in adults, in the treatment of the following bacterial infections due to levofloxacin-susceptible microorganisms:

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.*

Chronic bacterial prostatitis: due to *Eschericia 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* or *P. aeruginosa.*

Uncomplicated urinary tract infections in women: caused by *E. coli.*

Uncomplicated skin and skin structure infections: caused by *S. aureus, S. pyogenes, Acinetobacter calcoaceticus, E. cloacae, P. mirabilis, P. aeruginosa, E. coli, K. pneumoniae* or *S. faecalis.*

Complicated skin and skin structure infections: caused by *S. aureus, S. pyogenes, P. mirabilis, E. coli, K. pneumoniae, S. faecalis, E. cloacae* or *K. oxytoca.*

Intra-abdominal infections: caused by *E. coli* and anaerobic microorganisms.

4.2 Posology and method of administration

Posology

ZYBACT is to be taken once or twice daily in a usual dose of 250 mg or 500 mg. The dosage will depend on the type of pathogen and the severity of the infection. The use of ZYBACT 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 recommendation can be given for ZYBACT.

Daily dosage recommended in patients with normal renal function:

Acute exacerbation of chronic bronchitis: 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 days.

Chronic bacterial prostatitis: 500 mg once a day for 28 days.

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

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

Uncomplicated skin and skin structure infections: 250 – 500 mg once daily for 7 – 10 days.

Complicated skin and skin structure infections: 500 mg twice 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 where bacteraemia or septicaemia is present: 500 mg twice daily for 10 – 14 days.

Special populations

Daily dosage recommended in patients with impaired renal function

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

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

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

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

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

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

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

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

Patients with a creatinine clearance of less than 10 mL/min *or in patients on haemodialysis or CAPD (continuous ambulatory peritoneal dialysis):*

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

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

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

Elderly patients or patients with hepatic impairment

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

Method of administration

ZYBACT tablets should be swallowed whole, without crushing or chewing, as ZYBACT has a bad taste when crushed or chewed. ZYBACT tablets may be taken on an empty stomach or with meals. ZYBACT should be taken two hours before iron salts, antacids and sucralfate administration since reduction of absorption may occur.

4.3 Contraindications

The use of ZYBACT is contraindicated in:

- Patients with hypersensitivity to levofloxacin, other quinolones or to any of the excipients of ZYBACT listed in section 6.1.
- Epilepsy.

- Patients with a history of tendon disorders associated with fluoroquinolone administration.
- Children or adolescents (under 18 years of age).
- Pregnancy and lactation (see section 4.6).
- Concomitant use with tizanidine.
- Patients with confirmed mitral valve and aortic valve regurgitation unless no safer appropriate alternative is available, has failed or is not well tolerated.
- Concomitant use of fluroquinolones with angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) is contraindicated in patients with moderate to severe renal impairment (creatinine clearance ≤ 30 mL/min) and in elderly patients.

4.4 Special warnings and precautions for use

ZYBACT should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone- or fluoroquinolone-containing products (see section 4.8). Treatment of these patients with ZYBACT should only be initiated in the absence of alternative treatment options.

Hypersensitivity reactions:

ZYBACT can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema to anaphylactic shock) occasionally following the initial dose.

In the event of anaphylactic reactions, ZYBACT should be discontinued immediately. Medical treatment (therapy for shock) is imperative.

Prolonged, disabling and potentially irreversible serious adverse drug reactions:

Very rare 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. ZYBACT

should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

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

Concomitant use of fluoroquinolones and ACE inhibitors/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 fluoroquinolones or ACE inhibitors/ARBs whether used separately and/or concomitantly.

Risk of mitral and aortic regurgitation:

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

Aortic aneurysm and dissection:

There is some evidence of an increased risk of aortic aneurysm and dissection, particularly in elderly patients, after intake of fluoroquinolones. Fluoroquinolones such as ZYBACT 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. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis), or additionally vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren’s syndrome.

The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.

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

Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

QT interval prolongation:

Prolongation of the QT interval, sometimes progressing to torsades de pointes, has been associated with the use of ZYBACT. Therefore, ZYBACT should be avoided or used with caution in patients with known risk factors for prolongation of the QT interval such as:

- Congenital long QT syndrome.
- Uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia).
- Cardiac disease (e.g. heart failure, myocardial infarction, bradycardia).

Co-administration of ZYBACT with the following medicines should be avoided: Class IA antidysrhythmic medicines (e.g. quinidine or procainamide) or class III antidysrhythmic medicines (e.g. amiodarone or sotalol).
In addition, caution should be exercised when ZYBACT is used with other medicines known to have this effect, such as antimicrobial medicines (e.g. erythromycin or pentamidine), phenothiazines or tricyclic antidepressants (see section 4.5).

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

Clostridium difficile-associated disease (CDAD):

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

Hepato-biliary disorders:

Serious cases of hepatotoxicity, including fatalities, have been reported with fluoroquinolones, including ZYBACT, primarily in patients with severe underlying diseases. Patients should be advised to stop treatment if signs and symptoms of hepatic disease develop, such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

Peripheral neuropathy:

Peripheral sensory neuropathy and peripheral sensory motor neuropathy have been reported in patients receiving fluoroquinolones, including ZYBACT, which can be rapid in its onset. ZYBACT should be discontinued if the patient experiences symptoms of neuropathy such as pain, burning, tingling, numbness or weakness develop in order to prevent the development of an irreversible condition.

Tendinitis and tendon rupture:

Tendinitis, which may lead to tendon rupture, may rarely occur and most frequently involves the Achilles tendon. Tendinitis and tendon rupture, sometimes bilateral, may occur within 48 hours of starting treatment with ZYBACT and have been reported up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in patients aged over 60 years, in patients with renal impairment, patients with solid organ transplants, in patients receiving daily

doses of 1 000 mg and in patients using corticosteroids. Therefore, concomitant use of corticosteroids should be avoided. The daily dose should be adjusted in elderly patients based on creatinine clearance (see section 4.2). Close monitoring of these patients is therefore necessary if they are prescribed ZYBACT. If tendinitis is suspected, treatment with ZYBACT must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon. Corticosteroids should not be used if signs of tendinopathy occur.

Resistance:

Methicillin-resistant *Staphylococcus aureus* (MRSA) is very likely to possess co-resistance to fluoroquinolones, including levofloxacin. Therefore, ZYBACT 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, prescribers are advised to take into account the local prevalence of resistance in *E.coli* to fluoroquinolones.

Psychotic reactions:

Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin. In a few cases these have progressed to suicidal thoughts and self-endangering behaviour – sometimes after only a single dose of levofloxacin (see section 4.8).

In the event of psychotic side effects, ZYBACT must be discontinued immediately and the medical practitioner be consulted. ZYBACT should be used with caution in patients who are psychotic or who have a history of psychotic illness.

Severe cutaneous adverse reactions:

Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN; also known as Lyell's syndrome), Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with ZYBACT (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of these reactions appear, ZYBACT should be discontinued immediately and an alternative treatment should be considered. If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of levofloxacin, treatment with levofloxacin must not be restarted in this patient at any time.

Dysglycaemia:

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.

Renal impairment:

The dose of ZYBACT should be reduced in adult patients with renal impairment by reducing the total daily dose and/or by increasing the dosage interval in accordance with the creatinine clearance (see section 4.2). The plasma concentrations should ideally be monitored.

Seizures:

Caution should be exercised when using ZYBACT in patients prone to seizures, such as patients with pre-existing central nervous system lesions. The concomitant use of medicines which lower the cerebral seizure threshold, such as theophylline, should also be used with caution in these patients.

Caution should be exercised when using ZYBACT in patients being treated with fenbufen and

similar nonsteroidal anti-inflammatory medicines (NSAIDs). Concomitant use may increase the risk of central nervous system (CNS) stimulation and seizures.

Porphyria:

Fluoroquinolones, such as ZYBACT, have been known to trigger porphyria attacks (see section 4.8).

Glucose-6-phosphate dehydrogenase deficiency:

ZYBACT should be used with caution in patients with glucose-6-phosphate dehydrogenase deficiency.

Pseudomonas aeruginosa:

In the treatment of infections caused by *P. aeruginosa* (see section 4.1), an aminoglycoside should be administered concomitantly to minimise resistance to ZYBACT (see section 5.1).

Haematological disturbances:

Haematological disturbances including thrombocytopenia, eosinophilia, leucopenia, pancytopenia, haemolytic anaemia or agranulocytosis have been reported with ZYBACT.

Photosensitisation:

Photosensitisation has been reported with ZYBACT (see section 4.8). It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), during treatment and for 48 hours following treatment discontinuation 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 in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be

monitored when these medicines are given concomitantly (see section 4.5).

Myasthenia gravis:

ZYBACT should be used with caution in patients with myasthenia gravis, because the symptoms can be exacerbated.

Fluoroquinolones, including levofloxacin, 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. ZYBACT is not recommended in patients with a known history of myasthenia gravis.

Vision disorders:

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

Superinfection:

Fungal overgrowth and proliferation of other resistant microorganisms may occur. If superinfection occurs during therapy, appropriate measures should be taken.

Interference with laboratory tests:

Caution should be exercised when using ZYBACT in patients being tested for tuberculosis as ZYBACT inhibits the growth of *Mycobacterium tuberculosis* and therefore may give false-negative results in the bacteriological diagnosis of tuberculosis.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on ZYBACT

Iron salts, zinc salts, magnesium- or aluminium-containing antacids, didanosine:

The absorption of ZYBACT is significantly reduced when iron salts, or magnesium- or aluminium-

containing antacids, or didanosine (only didanosine formulations with aluminium- or magnesium-containing buffering agents) are administered concomitantly with ZYBACT. Concurrent administration of fluoroquinolones with multivitamins containing zinc appears to reduce their oral absorption. It is recommended that preparations containing divalent or trivalent cations such as iron salts, zinc salts or magnesium- or aluminium-containing antacids, or didanosine (only didanosine formulations with aluminium- or magnesium-containing buffering medicines) should not be taken 2 hours before or after ZYBACT administration (see section 4.2). Calcium salts have a minimal effect on the oral absorption of levofloxacin.

Sucralfate:

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

Theophylline, fenbufen or similar nonsteroidal 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:

Probenecid and cimetidine had a statistically significant effect on the elimination of levofloxacin. The renal clearance of levofloxacin was reduced by cimetidine (24 %) and probenecid (34 %). This is because both medicines are capable of blocking the renal tubular secretion of levofloxacin. However, at the tested doses in the study, the statistically significant kinetic differences are unlikely

to be of clinical relevance.

Caution should be exercised when levofloxacin is coadministered with medicines that affect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

Other relevant information:

Clinical pharmacology studies have shown that the pharmacokinetics of levofloxacin were not affected to any clinically relevant extent when levofloxacin was administered together with the following medicines: calcium carbonate, digoxin, glibenclamide, ranitidine.

Effect of ZYBACT on other medicines

Ciclosporin:

The half-life of ciclosporin was increased by 33 % when coadministered with levofloxacin.

Vitamin K antagonists:

Increased coagulation tests (PT/INR) and/or bleeding, which may be severe, have been reported in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin). Coagulation tests, therefore, should be monitored in patients treated with vitamin K antagonists (see section 4.4).

Medicines known to prolong QT interval:

ZYBACT, like other fluoroquinolones, 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, 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 is not a CYP1A2

inhibitor.

Other forms of interactions

Angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers:

Concomitant use of fluoroquinolones and ACE inhibitors/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).

Meals:

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

4.6 Fertility, pregnancy and lactation

Pregnancy

In the absence of human data and since experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism ZYBACT is contraindicated in, and must not be used during pregnancy (see section 4.3).

Breastfeeding

ZYBACT is contraindicated in breastfeeding women. There is insufficient evidence on the excretion of levofloxacin in human milk, however other fluoroquinolones are excreted in human breast milk (see section 4.3).

Fertility

Levofloxacin caused no impairment of fertility or reproductive performance in rats.

4.7 Effects on ability to drive and use machines

Some undesirable effects (e.g. dizziness/vertigo, drowsiness, visual disturbances) may impair the

patient's ability to concentrate and react, and therefore may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

4.8 Undesirable effects

System organ class	Frequent	Less frequent	Not known (cannot be estimated from available data)
Infections and infestations		Fungal infection including Candida infection Pathogen resistance	
Blood and lymphatic system disorders		Thrombocytopenia Neutropenia Leukopenia Eosinophilia	Pancytopenia Agranulocytosis Haemolytic anaemia
Immune system disorders		Angioedema Hypersensitivity (see section 4.4)	Anaphylactic[a] shock Anaphylactoid[a] shock (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 Confusional state Nervousness Psychotic reactions (with hallucination,	Psychotic disorder with self-endangering behaviour including suicidal ideation or suicide attempt (see

		paranoia) Depression Agitation Abnormal dreams Nightmares	section 4.4)
Nervous system disorders*	Headache Dizziness	Somnolence Tremor Dysgeusia Convulsion (see sections 4.3 and 4.4) Paraesthesia	Peripheral sensory neuropathy (see section 4.4) Peripheral sensory motor neuropathy (see section 4.4) Parosmia including anosmia Dyskinesia Extrapyramidal disorder Ageusia Syncope Benign intracranial hypertension
Eye disorders*		Visual disturbances such as blurred vision (see section 4.4)	Transient vision loss (see section 4.4)
Ear and labyrinth disorders*		Vertigo Tinnitus	Hearing loss Hearing impaired
Cardiac disorders**		Tachycardia Palpitation	Ventricular tachycardia, which may result in cardiac arrest Ventricular dysrhythmia

			and torsade de pointes (reported predominantly in patients with risk factors of QT prolongation), Electrocardiogram QT prolonged (see sections 4.4)
Vascular disorders**		Hypotension	
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Bronchospasm Pneumonitis allergic
Gastrointestinal disorders	Diarrhoea Vomiting Nausea	Abdominal pain Dyspepsia Flatulence Constipation	Diarrhoea – haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis (see section 4.4) Pancreatitis
Hepato-biliary 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[b]		Rash Pruritus Urticaria Hyperhidrosis Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4) Fixed drug eruption	Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Photosensitivity reaction (see section 4.4) Leukocytoclastic vasculitis Stomatitis
Endocrine disorders		Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)	
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	Rhabdomyolysis Tendon rupture (e.g. Achilles tendon) (see sections 4.3 and 4.4) Ligament rupture Muscle rupture Arthritis

		section 4.4])	
Renal and urinary disorders		Blood creatinine increased Renal failure acute (e.g. due to interstitial nephritis)	
General disorders and administration site conditions*		Asthenia Pyrexia	Pain (including pain in back, chest, and extremities)

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

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

* 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 aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones) have been reported in patients taking fluoroquinolones (see section 4.4).

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

- Attacks of porphyria in patients with porphyria (see section 4.4).

Post-marketing experience

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 fluoroquinolone use was the causative factor, or a contributory factor or played no role in the reported cases where mitral cases and/or aortic regurgitation was diagnosed.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of ZYBACT is important. It allows continued monitoring of the benefit/risk balance of ZYBACT. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms:

The symptoms that can be expected from an overdosage of ZYBACT are central nervous system symptoms (such as confusion, dizziness, impairment of consciousness and convulsive seizures) and gastrointestinal reactions (such as nausea and mucosal erosions). In clinical pharmacology studies performed with a supra-therapeutic dose, increase in QT interval has been seen.

Treatment:

The treatment of an overdosage is symptomatic and supportive.

In the event of overdose, the patients should be carefully observed (including ECG monitoring). Antacids may be used for protection of gastric mucosa. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body. No specific antidote exists.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.1.1 Broad and medium spectrum antibiotics.

Pharmacotherapeutic group: Quinolone antibacterials – fluoroquinolones.

ATC code: J01MA12.

Levofloxacin is a broad-spectrum bactericidal fluoroquinolone. Levofloxacin is the pure (-) (*S*) enantiomer of ofloxacin.

The bactericidal action of levofloxacin results from interference with the enzymes topoisomerase IV and DNA gyrase, which are needed for 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. Acquired resistance: Resistant strains, particularly of methicillin-resistant *S. aureus* (MRSA), *P. aeruginosa, E. coli, K. pneumoniae, C. jejuni, N. gonorrhoeae* and *S. pneumoniae* have emerged during treatment with levofloxacin, although there are widely differing patterns of resistance geographically.

5.2 Pharmacokinetic properties

Absorption:

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

Distribution, metabolism and excretion:

Levofloxacin is approximately 30 – 40 % bound to serum protein. Steady state is achieved within 3 days. Levofloxacin is metabolised to a small degree to inactive metabolites, being desmethyl levofloxacin and levofloxacin *N*-oxide. The elimination half-life of levofloxacin is 6 – 8 hours after oral administration. Levofloxacin is excreted largely unchanged, primarily via the kidney.

Distribution in tissues and fluids:

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone

Hypromellose

Instacoat ICG-U-10236 Pink (containing hypromellose, macrogol, red iron oxide, talc, titanium dioxide, yellow iron oxide)

Microcrystalline cellulose

Sodium stearyl fumarate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

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

Keep blister strips in outer container until required for use.

6.5 Nature and contents of container

Transparent PVC/PVDC/aluminium blister strips, inside an outer cardboard box.

Pack sizes: 5 or 10 tablets.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion 0157

8. REGISTRATION NUMBERS

ZYBACT 250 mg: 44/20.1.1/0249

ZYBACT 500 mg: 44/20.1.1/0250

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

19 April 2013

10. DATE OF REVISION OF THE TEXT

06 November 2024