LEVOQUIN 250 / 500

COMPOSITION

LEVOQUIN 250:

Active Ingredient: Each film – coated caplet contains levofloxacin hemihydrate equivalent to 250 mg of levofloxacin.

LEVOQUIN 500:

Active Ingredient: Each film – coated caplet contains levofloxacin hemihydrate equivalent to 500 mg of levofloxacin.

Other Ingredients: Maize starch, lactose, croscarmellose sodium, povidone, sodium starch glycolate, magnesium stearate, colloidal silicon dioxide, HPMC, PEG 6000, titanium dioxide, quinoline yellow and purified water.

PHARMACODYNAMICS

Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination.

PHARMACOKINETICS

✓ ***Absorption***

Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1 h. The absolute bioavailability is approximately 100 %.

Food has little effect on the absorption of levofloxacin.

✓ ***Distribution***

Approximately 30 - 40 % of levofloxacin is bound to serum protein. 500 mg once daily multiple dosing with levofloxacin showed negligible accumulation. There is modest but predictable accumulation of levofloxacin after doses of 500 mg twice daily. Steady-state is achieved within 3 days.

Penetration into Bronchial Mucosa, Epithelial Lining Fluid (ELF)

Maximum levofloxacin concentrations in bronchial mucosa and epithelial lining fluid after 500 mg p.o. were 8.3 µg/g and 10.8 µg/ml respectively. These were reached approximately one hour after administration.

Penetration into Lung Tissue

Maximum levofloxacin concentrations in lung tissue after 500 mg p.o. were approximately 11.3 µg/g and were reached between 4 and 6 hours after administration. The concentrations in the lungs consistently exceeded those in plasma.

Penetration into Blister Fluid

Maximum levofloxacin concentrations of about 4.0 and 6.7 µg/ml in the blister fluid were reached 2 - 4 hours after administration following 3 days dosing at 500 mg once or twice daily, respectively.

Penetration into Cerebro-Spinal Fluid

Levofloxacin has poor penetration into cerebro-spinal fluid.

Penetration into prostatic tissue

After administration of oral 500mg levofloxacin once a day for three days, the mean concentrations in prostatic tissue were 8.7µg/g, 8.2 µg/g and 2.0 µg/g respectively after 2 hours, 6 hours and 24 hours; the mean prostate/plasma concentration ratio was 1.84.

Concentration in urine

The mean urine concentrations 8 -12 hours after a single oral dose of 150 mg, 300 mg or 500 mg levofloxacin were 44 mg/L, 91 mg/L and 200 mg/L, respectively.

✓ ***Metabolism***

Levofloxacin is metabolized 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.

✓ ***Excretion***

Following oral and intravenous administration of levofloxacin, it is relatively eliminated slowly from the plasma (t1/2: 6-8 h). Excretion is primarily by renal route (> 85% of administered dose).

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

INDICATIONS

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Acute maxillary sinusitis, community-acquired pneumoniae (CAP), uncomplicated skin and skin structure infections (mild and moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections, complicated UTI (mild and moderate), acute pyelonephritis (mild and moderate).

The following indication(s), should be restricted:

- Acute bacterial rhinosinusitis*
- Acute bacterial exacerbation of chronic bronchitis (ABECB)*

* *Levofloxacin should be only used:*

+ When *Pseudomonas* is considered and the patient is allergic to antipseudomonal penicillins/ cephalosporins;
+ For resistant organisms with no other alternative antibiotics available.

CONTRAINDICATIONS

Levofloxacin is contraindicated in persons with known hypersensitivity to levofloxacin, or other quinolone antibacterials or any of the product components.

WARNINGS AND PRECAUTIONS

Aortic aneurysm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.

Therefore, fluoroquinolones 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 physician in an emergency department.

The use of levofloxacin should be avoided in patients who have experienced serious adverse reactions in the

past when using fluoroquinolones containing products (see section Side effects).

Treatment of these patients levofloxacin should be initiated in the absence of alternative treatment options and after careful benefit/ risk assessment.

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 fluoroquinolones irrespective of their age and pre-existing risk factors.

Levofloxacin 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.

Tendinopathy and Tendon Rupture: Fluoroquinolones, including levofloxacin, are associated with an increased risk of tendonitis and tendon rupture in all ages.

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 fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients (above 60 years of age), with renal impairment, patients with solid organ transplants, those treated concurrently with corticosteroids and patients receiving daily doses of 1000 mg levofloxacin. Therefore, concomitant use of corticosteroids should be avoided.

At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with levofloxacin should be discontinued and alternative treatment should be considered. The affected limb (so should be appropriately treated (e.g. immobilisation). Corticorsteroids should not be used if signs of tendinopathy occur.

Hypersensitivity Reactions: Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones, including levofloxacin.

Hepatotoxicity: Post-marketing reports of severe hepatotoxicity (including acute hepatitis and fatal events) have been received for patients treated with levofloxacin.

Central Nervous System Effects: Convulsions and toxic psychoses have been reported in patients receiving fluoroquinolones, including levofloxacin.

***Clostridium difficile*-Associated Diarrhea:** *Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including levofloxacin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*

Peripheral Neuropathy: Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with levofloxacin should be advised to inform their doctor and pharmacist prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition (see section Side effects).

Prolongation of the QT Interval: Some fluoroquinolones, including levofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia.

Blood Glucose Disturbances: As with other fluoroquinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with levoquin.

Photosensitivity/Phototoxicity: Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with the use of fluoroquinolones after sun or UV light exposure. **Exacerbation of myasthenia gravis:** Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in person with myasthenia gravis. Post marketing serious adverse events, including deaths and requirement for ventilator support have been associated with fluoroquinolones use in persons with myasthenia gravis. Avoid fluoroquinolones in patients with known history of myasthenia gravis.

Psychiatric reactions

Psychiatric reactions may occur even after the first administration of fluoroquinolones, including Levoquin. In rare cases, depression or psychotic reactions can progress to suicidal ideations/thoughts and self-injurious behaviour, such as attempted or completed suicide (see section 'Side Effects'). In the event that the patient develops these reactions, Levoquin should be discontinued and appropriate measures instituted. Caution is recommended if Levoquin is to be used in psychotic patients or in patients with a history of psychiatric disease.

INTERACTION WITH OTHER DRUGS

✓ **Antacids, Sucralfate, Metal Cations, Multivitamins:** These agents should be taken at least two hours before or two hours after levofloxacin administration.

✓ **Theophylline:** Concomitant administration of other quinolones with theophylline has resulted in prolonged elimination half-life, elevated serum theophylline levels.

✓ **Warfarin:** Elevations of the prothrombin time in the setting of concurrent warfarin and levofloxacin use have been associated with episodes of bleeding.

✓ **Cyclosporine:** No dosage adjustment is required for levofloxacin or cyclosporine when administered concomitantly.

✓ **Digoxin:** Levofloxacin absorption and disposition kinetics were similar in the presence or absence of digoxin.

✓ **Probenecid and Cimetidine:** The AUC and T1/ 2 of levofloxacin were 27-38% and 30% higher, respectively, while CL/ F and CLR were 21-35% lower during concomitant treatment with probenecid or cimetidine compared to levofloxacin alone. Although these differences were statistically significant, the changes were not high enough to warrant dosage adjustment for levofloxacin when probenecid or cimetidine is co- administered.

✓ **Non-steroidal anti-inflammatory drugs:** The concomitant adminis-tration of a non-steroidal anti-inflammatory drug with a quinolone, including levofloxacin, may increase the risk of CNS stimulation and convulsive seizures.

✓ **Antidiabetic agents:** Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with quinolones and an antidiabetic agent.

DOSAGE AND ADMINISTRATION

Adult ≥ 18 years: 250 – 500 mg PO every 24 hours.

ABECB: 500 mg every 24 hours for 7 days.

CAP: 500 mg every 24 hours for 7 – 14 days.

Acute maxillary sinusitis: 500 mg every 24 hours for 10 – 14 days.

Uncomplicated skin and skin structure infections: 500 mg every 24 hours for 7 – 10 days.

Complicated UTI and/or acute pyelonephritis: 250 mg every 24 hours for 10 days.

PREGNANCY AND LACTATION

Pregnancy

No adequate and well-controlled studies in pregnant women. Levofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

Levofloxacin has not been measured in human milk. Based upon data from ofloxacin, it can be presumed that levofloxacin will be excreted in human milk. Because of the potential for serious adverse reactions from levofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

SIDE EFFECTS

Post Marketing Experience

Exacerbation of myasthenia gravis

Allergic reactions

Uncommon: pruritus, rash.

Rare: urticaria, bronchospasm/dyspnoea.

Very rare: angio-oedema, hypotension, anaphylactic-like shock; photosensitization.

Isolated cases: severe bullous eruptions such as Stevens Johnson syndrome, toxic pidermal necrolysis (Lyell's syndrome) and erythema exsudativum multiforme. Muco-cutaneous, anaphylactic/-oid reactions may sometimes occur even after the first dose.

Gastro-intestinal, metabolism

Common: nausea, diarrhea.

Uncommon: anorexia, vomiting, abdominal pain, dyspepsia.

Rare: bloody diarrhoea which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis.

Very rare: hypoglycaemia, particularly in diabetic patients.

Nervous system disorders and psychiatric disorders*

Uncommon: headache, dizziness/vertigo, drowsiness, insomnia.

Rare: depression, psychotic reactions (with e.g. hallucinations, paranoia), paraesthesia, tremor, anxiety, agitation, confusion, convulsions.

Very rare: hypoaesthesia, visual and auditory disturbances, disturbances of taste and smell, psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide).

Not known (cannot be estimated from available data): Psychotic disorders with self-endangering behavior including suicidal ideation or suicide attempt.

Isolated cases: Psychotic reactions with self endangering behaviour including suicidal ideation or acts.

Cardiovascular

Rare: tachycardia, hypotension

Very rare: shock (anaphylactic/-oid)

Isolated cases: QT-interval prolongation

Musculoskeletal and connective tissue disorders*

Rare: arthralgia, myalgia, tendon disorders including tendinitis (e.g. Achilles tendon).

Very rare: tendon rupture (e.g. Achilles tendon), as with other fluoroquinolones this undesirable effect may occur within 48 hours of starting treatment and may be bilateral; Muscular weakness, which may be of special importance in patients with myasthenia gravis.

Isolated cases: rhabdomyolysis.

Liver, kidney

Common: increased liver enzyme levels (e.g. ALT, AST).

Uncommon: increase in bilirubin, increase in serum creatinine.

Very rare: liver reactions such as hepatitis acute kidney failure (e.g. due to interstitial nephritis).

Blood

Uncommon: eosinophilia, leucopenia.

Rare: neutropenia, thrombocytopenia.

Very rare: agranulocytosis.

Isolated cases: haemolytic anaemia, pancytopenia.

Eye disorders*

Very rare: visual disturbances.

Ear and labyrinth disorders*

Very rare: auditory disturbances.

General disorders and administrative site conditions*

Uncommon: asthenia, fungal overgrowth and proliferation of other resistant microorganisms.

Very rare: allergic pneumonitis, fever.

* Very rare cases if 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 associated with the use of fluoroquinolones in some cases irrespective of pre-existing risk factors (see section Warnings and Precautions).

OVERDOSE AND TREATMENT

Levofloxacin exhibits a low potential for acute toxicity. In the event of an acute overdosage, the stomach should be emptied. The patient should be observed and appropriate hydration maintained. Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

SHELF LIFE AND STORAGE INSTRUCTIONS

The expiry date of this medicinal product is printed on the box and blister foil. Do not use this medicinal product after the expiry date.

Storage condition: In a dry, cool place (< 30°C). Protect from light.

KEEP DRUG OUT OF REACH OF CHILDREN.

CAREFULLY READ THE PACKAGE INSERT BEFORE USE.

PREPARATIONS AND PACK SIZE

LEVOQUIN 250:

LEVOQUIN 250 film-coated caplet appears as plain, oblong, yellow film-coated tablets.

LEVOQUIN 250 are provided in pack sizes of 12 caplets.

LEVOQUIN 500:

LEVOQUIN 500 film – coated caplet appears as yellow film – coated caplet, engraved "P" on one side.

LEVOQUIN 500 are provided in pack sizes of 8 caplets.

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Manufacturer

PYMEPHARCO JOINT STOCK COMPANY

(PYMEPHARCO is a subsidiary of STADA ARZNEIMITTEL AG)

166-170 Nguyen Hue Str., Tuy Hoa City, Phu Yen Province, Vietnam.