SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oflox 400 Tablets*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg ofloxacin.

Excipients with known effects: 333 mg lactose per tablet.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Pale, yellowish-white coloured, capsule shaped, biconvex, film-coated tablets with central breakline on one side and plain on other side.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication:

Oflox 400 Tablets is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.*

Oflox 400 Tablets is only indicated as a second-line antimycobacterial drug when use of first line drugs is not appropriate due to resistance or intolerance, and should only be used when other recommended fluoroquinolone options are not available.

Consideration should be given to official treatment guidelines for tuberculosis, e.g those of WHO: (http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf).

4.2 Posology and method of administration

Adults and adolescents:
The recommended dose is 400 mg twice daily.

Children:
The recommended dose is 15-20 mg/kg/day, divided into two daily doses, up to a maximum of 800 mg/day.

Renal impairment:
For patients with an estimated creatinine clearance ≤ 30 ml/min, with or without haemodialysis, the dose should be reduced to 600-800 mg given three times per week.

Hepatic impairment:
Limited data suggest that, due to the hepato-renal syndrome, the excretion of ofloxacin may be reduced in patients with severe hepatic dysfunction (see also section 5.2).

* Trade names are not prequalified by WHO. This is under local drug regulatory authority's responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

Elderly
No adjustment of dosage is required in the elderly, other than that imposed by consideration of renal function.

Method of administration
Oflox 400 Tablets should be swallowed whole with a sufficient amount of liquid. The tablets may be taken without regard to food

4.3 Contraindications

Oflox 400 Tablets is contraindicated:
- in patients with hypersensitivity to ofloxacin, other quinolones or to any of the excipients
- in patients with epilepsy
- in patients with history of tendon disorders related to fluoroquinolone administration
- in breast-feeding women

4.4 Special warnings and precautions for use

Tendinitis and tendon rupture
Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. The risk of tendinitis and tendon rupture is increased in the elderly and in patients using corticosteroids. Close monitoring of these patients is therefore necessary if they are prescribed Oflox 400 Tablets. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with Oflox 400 Tablets must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

Clostridium difficile-associated disease
Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with Oflox 400 Tablets, may be symptomatic of *Clostridium difficile*-associated disease, the most severe form of which is pseudomembranous colitis. If pseudomembranous colitis is suspected, Oflox 400 Tablets must be stopped immediately and patients should be treated with supportive measures ± specific therapy without delay (e.g. oral vancomycin). Products inhibiting peristalsis are contraindicated in this clinical situation.

Patients predisposed to seizures
Oflox 400 Tablets are contraindicated in patients with a history of epilepsy and, as with other quinolones, should be used with caution in patients predisposed to seizures, such as patients with pre-existing central nervous system lesions, concomitant treatment with fenbufen and similar non-steroidal anti-inflammatory drugs, or with drugs which lower the cerebral seizure threshold, such as theophylline (see section 4.5). In case of convulsive seizures, treatment with ofloxacin should be discontinued.

Patients with G-6- phosphate dehydrogenase deficiency
Patients with latent or manifest defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents, and so ofloxacin should be used with caution.

Patients with renal impairment
Since ofloxacin is excreted mainly by the kidneys, the dose of Oflox 400 Tablets should be adjusted in patients with renal impairment (see section 4.2).

Hypersensitivity reactions
Ofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema up to anaphylactic shock), occasionally following the initial dose (see section 4.8). Patients should discontinue treatment immediately.

Hypoglycaemia
As with all quinolones, hypoglycaemia has been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. glibenclamide) or with insulin. In these diabetic patients, careful monitoring of blood glucose is recommended. (See section 4.8).

Prevention of photosensitisation
Although photosensitisation is very rare with ofloxacin, it is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV light (e.g. sunray lamp, solarium), 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 Oflox 400 Tablets in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomitantly (see section 4.5).

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

QT interval prolongation
Caution should be taken when using fluoroquinolones, including ofloxacin, in patients with known risk factors for prolongation of the QT interval such as:
- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, methadone).
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- elderly
- preexisting cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

Peripheral neuropathy
Sensory or sensorimotor peripheral neuropathy has been reported in patients receiving fluoroquinolones, which can be rapid in its onset. If the patient experiences symptoms of neuropathy, Oflox 400 Tablets may be continued only when the benefits are considered to outweigh the risk of irreversible neuropathy.

Patients with myasthenia gravis
Ofloxacin should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Opiates
In patients treated with ofloxacin, determination of opiates in urine may give false-positive results. It may be necessary to confirm positive opiate screens by a more specific method.

Hepatobiliary disorders
Cases of hepatic necrosis, including life threatening hepatic failure, have been reported with ofloxacin, primarily in patients with severe underlying diseases, e.g. sepsis (see section 4.8). Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

Paediatric population
Due to adverse effects on the cartilage in juvenile animals (see section 5.3), and to limited documentation of the safety and appropriate dose adjustments, ofloxacin should only be used in children and adolescents with *M. Tuberculosis* infection if the benefit is considered to exceed the risk and there are no treatment alternatives.

Patients with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption
Oflox 400 Tablets contains a small amount of lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption may experience symptoms of intolerance.

4.5 Interaction with other medicinal products and other forms of interaction

Iron salts, magnesium- or aluminium-containing antacids
Ofloxacin absorption is significantly reduced when iron salts, or magnesium- or aluminium-containing antacids are administered concomitantly with Oflox 400 Tablets. It is recommended that preparations containing divalent or trivalent cations such as iron salts, or magnesium- or aluminium-containing antacids should not be taken within 2 hours before or after Oflox 400 Tablets tablet administration. No interaction was found with calcium carbonate.

Sucralfate
The bioavailability of ofloxacin is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and Oflox 400 Tablets, it is best to administer sucralfate at least 2 hours after the Oflox 400 Tablets tablet administration.

Theophylline
No pharmacokinetic interactions of ofloxacin 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.

NSAIDs
Coadministration with nonsteroidal anti-inflammatory drugs (NSAIDs) may potentiate the risk of central nervous system toxicity sometimes associated with fluoroquinolone use. The interaction has been reported most often with enoxacin. It may occur with other fluoroquinolones as well, but is poorly documented. Patients with a history of seizures may be at greater risk. (see also section 4.4.)

Vitamin K antagonists
Increases in coagulation parameters (as measured e.g. by PT/INR) and/or bleeding, which may be severe, have been reported in patients treated with ofloxacin in combination with a vitamin K antagonist (e.g. warfarin). Therefore, coagulation parameters should be monitored in patients treated with vitamin K antagonists (see section 4.4).

Drugs known to prolong QT interval
Ofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, methadone). (See section 4.4 “QT interval prolongation”).

Drugs undergoing renal tubular secretion:
With high doses of quinolones, impairment of excretion and an increase in serum levels may occur when co-administered with other drugs that undergo renal tubular secretion (e.g. probenecid, cimetidine, frusemide and methotrexate).

4.6 Fertility, pregnancy and breast-feeding

Women of childbearing potential:
Pregnancy should be avoided in women treated with ofloxacin. Adequate contraceptive measures should be taken.

Pregnancy
There are limited data from the use of ofloxacin in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).
However in the absence of human data and due to experimental data suggesting a risk of damage to the weight-bearing cartilage of the growing organism by fluoroquinolones, ofloxacin should only be used in pregnancy if the benefit is considered to outweigh the risks, and there are no available treatment alternatives.

Lactation
Ofloxacin is contraindicated in breast-feeding women. Ofloxacin was found in human milk at concentrations about equal to maternal serum levels. Due to experimental data suggesting a risk of damage to the weight-bearing cartilage of the growing organism by fluoroquinolones, Oflox 400 Tablets must not be used in breast-feeding women (section 5.3).

Fertility
Ofloxacin caused no impairment of fertility or reproductive performance in rats.

4.7 Effects on ability to drive and use machines

No studies on the effects of ofloxacin on the ability to drive and use machines have been performed. 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

Adverse events considered at least possibly related to ofloxacin treatment are listed below by body system, organ class and frequency. Frequency estimates are in many cases not based on adequately sized randomised trials, but on published data generated during post-approval use. Sometimes, no frequency data can be given. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1000 to <1/100), rare (≥ 1/10000 to <1/1000), very rare (<1/10000), 'not known' (frequency can not be estimated from the available data). Note that the frequencies relate to short-term therapy (<1 month).

Infections and infestations
Uncommon: fungal infection (and proliferation of other resistant microorganisms of the normal flora)

Blood and lymphatic system disorders
Very rare: anaemia, haemolytic anaemia, leukopenia, eosinophilia, thrombocytopenia
Not known: agranulocytosis, bone marrow failure

Immune system disorders
Rare: Anaphylactoid reaction, angioedema
Very rare: anaphylactic shock (see section 4.4) Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose.

Metabolism and nutrition disorders
Rare: anorexia
Not known: hypoglycaemia, particularly in diabetic patients (see section 4.4)

Psychiatric disorders
Uncommon: agitation, sleep disorder, insomnia
Rare: psychotic disorder, depression, confusional state, anxiety, nightmares
Very rare: psychotic reactions with self-endangering behaviour including suicidal ideation or acts (see section 4.4), hallucination

Nervous system disorders
Uncommon: dizziness, headache
Rare: somnolence, paraesthesia, dysgeusia, parosmia
Very rare: peripheral sensory neuropathy, convulsions, extrapyramidal symptoms or other disorders of muscular coordination

Eye disorders
Uncommon: eye irritation
Rare: visual disturbance

Ear and Labyrinth disorders
Uncommon: vertigo
Very rare: tinnitus, hearing loss

Cardiac disorders
Rare: tachycardia
Not known: ventricular arrhythmias, torsade des pointes (see section 4.4 “QT interval prolongation” and section 4.9)

Vascular disorders
Rare: hypotension

Respiratory, thoracic and mediastinal disorders
Uncommon: cough, nasopharyngitis
Rare: bronchospasm, dyspnoea
Not known: Allergic pneumonitis, severe dyspnoea

Gastrointestinal disorders
Uncommon: abdominal pain, diarrhoea, nausea, vomiting
Rare: enterocolitis, sometimes haemorrhagic
Very rare: pseudomembranous colitis

Hepatobiliary disorders
Rare: hepatic enzymes increased (ALT, AST, LDH, GGT and/or alkaline phosphatase), blood bilirubin increased
Very rare: cholestatic jaundice
Not known: hepatitis, which may be severe (see section 4.4)

Skin and subcutaneous tissue disorders
Uncommon: rash, pruritus
Rare: urticarial, hot flushes, hyperhidrosis, pustular rash
Very rare: erythema multiforme, toxic epidermal necrolysis, photosensitivity reaction, drug eruption, vascular purpura, vasculitis, in exceptional cases with skin necrosis
Not known: Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, drug rash

Musculoskeletal and Connective tissue disorders
Rare: tendinitis
Very rare: arthralgia, myalgia, tendon rupture (see section 4.4). This undesirable effect may occur within 48 hours of starting treatment and may be bilateral.
Not known: rhabdomyolysis and/or myopathy, muscular weakness, muscle tear, muscle rupture

Renal and urinary disorders
Rare: serum creatinine increased
Very rare: acute renal failure (e.g. due to interstitial nephritis)

Other undesirable effects which have been associated with fluoroquinolone administration include:
- extrapyramidal symptoms and other disorders of muscular coordination
- hypersensitivity vasculitis
- attacks of porphyria in patients with porphyria

4.9 Overdose

According to toxicity studies in animals or clinical pharmacology studies performed with supra-therapeutic doses, the most important signs to be expected following acute overdosage of Oflox 400 Tablets 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.
There is no specific antidote. In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Antacids may be used for protection of gastric mucosa. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing ofloxacin from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial for systemic use, fluoroquinolone.
ATC code: J01MA01

Ofloxacin is a synthetic antibacterial agent of the fluoroquinolone class. It is a racemic mixture of 50% levofloxacin, which is the main biologically active component, and 50% dextrofloxacin.

Mechanism of action
Ofloxacin has *in vitro* activity against *M. Tuberculosis*, as well as against a wide range of Gram-positive and Gram-negative pathogens. The bactericidal action of ofloxacin against *M. Tuberculosis* results from the inhibition of the DNA gyrase, encoded by the *gyrA* and *gyrB* genes.

The wild-type ofloxacin MIC distribution for clinical isolates of *M. Tuberculosis* has been reported by different investigators to range between 0.25-2 mg/l. When resistance to fluoroquinolones arises, it is generally caused by mutations in *gyrA.* Cross-resistance within the fluoroquinolone drug class is extensive, though not universal.

Clinical efficacy
Experience of MDR-TB treatment with ofloxacin within clinical trials is limited.

5.2 Pharmacokinetic properties

Absorption and Bioavailability
Following oral administration, the bioavailability of ofloxacin is approximately 98%. Maximum serum concentrations are achieved one to two hours after an oral dose.
Food has little effect on the extent of absorption of ofloxacin.

Following single dose administration of Oflox 400 Tablets in healthy volunteers, the mean (±SD) ofloxacin Cmax value was 5.77 µg/ml (±1.28) and the corresponding value for AUC was 38.51 µg.h/ml (±4.48). The median (±SD) ofloxacin Tmax value was 1.02 (±0.52) hours.

Distribution
In vitro, approximately 32% of the drug in plasma is protein bound.

Elimination
Between 65% and 80% of an administered oral dose of ofloxacin is excreted unchanged via the kidneys within 48 hours of dosing. Studies indicate that less than 5% of an administered dose is recovered in the urine as the desmethyl- or N-oxide metabolites. Four to eight percent of an ofloxacin dose is excreted in the faeces. This indicates a small degree of biliary excretion of ofloxacin.

Renal insufficiency
Clearance of ofloxacin is reduced in patients with impaired renal function, and dosage adjustment is necessary (se section 4.2.)

Decompensated liver disease
A decrease in renal clearance of ofloxacin by 60% has been reported in patients with decompensated liver disease, compared to healthy controls. This was not related to decreased estimated creatinine clearance, and may have been due to decreased tubular secretion.

5.3 Preclinical safety data

Ofloxacin, as well as other drugs of the quinolone class, has been shown to cause arthropathies (arthrosis) in immature dogs and rats. In addition, these drugs are associated with an increased incidence of osteochondrosis in rats as compared to the incidence observed in vehicle-treated rats. There is no evidence of arthropathies in fully mature dogs at intravenous doses up to 3 times the recommended maximum human dose (on a mg/m2 basis or 5 times based on mg/kg basis), for a one-week exposure period.

Long-term, high-dose systemic use of other quinolones in experimental animals has caused lenticular opacities; however, this finding was not observed in any animal studies with ofloxacin.

Reduced serum globulin and protein levels were observed in animals treated with other quinolones. In one ofloxacin study, minor decreases in serum globulin and protein levels were noted in female cynomolgus monkeys dosed orally with 40 mg/kg ofloxacin daily for one year. These changes, however, were considered to be within normal limits for monkeys.

Crystalluria and ocular toxicity were not observed in any animals treated with ofloxacin.

Long-term studies to determine the carcinogenic potential of ofloxacin have not been conducted.

Ofloxacin was not mutagenic in the Ames bacterial test, in vitro and in vivo cytogenetic assay, sister chromatid exchange (Chinese Hamster and Human Cell Lines), unscheduled DNA Repair (UDS) using human fibroblasts, dominant lethal assays, or mouse micronucleus assay. Ofloxacin was positive in the UDS test using rat hepatocytes and Mouse Lymphoma Assay.

In reproductive studies in rats and rabbits, ofloxacin did not cause an increase in birth defects in either species. The highest dose (1600 mg/kg in rats and 160 mg/kg in rabbits) produced maternal and fetal toxicity in both species. Ofloxacin and other quinolones are toxic to developing cartilage in animal studies. Fertility in rats was not affected at doses of up to 360 mg/kg in either males or females.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Core tablet: Corn starch, hydroxypropyl cellulose, lactose anhydrous, magnesium stearate and sodium starch glycolate.
Film coat (Opadry yellow O4F52565): Hypromellose, iron oxide yellow, polyethylene glycol and titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30^{o}C.

6.5 Nature and contents of container

Blister pack
PVC-Al blister pack containing 100 (10 x 10) tablets per pack.

Bottle packs

- 150 cc HDPE bottle with 38 mm screw cap containing 1 g silica gel bag (desiccant) and rayon sani coil (filler), containing 100 tablets
- 750 cc HDPE bottle with 53 mm screw cap containing 5 g silica gel bag (desiccant) and rayon sani coil (filler), containing 500 tablets
- 1500 cc HDPE bottle with 89 mm screw cap containing 5 g silica gel bag (desiccant) and rayon sani coil (filler), containing 1000 tablets

6.6 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed off in accordance with local requirements.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)

TB225

9. DATE OF FIRST PREQUALIFICATION/ LAST RENEWAL

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10. DATE OF REVISION OF THE TEXT:

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