SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT
Moxifloxacin 400mg tablets*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains moxifloxacin hydrochloride equivalent to 400 mg moxifloxacin.

Excipients with known effects: 50 mg lactose monohydrate per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.

Brick-red coloured, capsule shaped, biconvex, film-coated tablets, plain on both the sides.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications:
Moxifloxacin 400mg tablets is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by Mycobacterium tuberculosis.

Moxifloxacin 400mg tablets is only indicated as a second-line antimycobacterial drug when use of first line drugs is not appropriate due to resistance or intolerance.

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
Oral use

Posology
Adults, adolescents and children weighing at least 33 kg:
The dose of Moxifloxacin 400mg tablets is one 400 mg tablet once daily.

Children: Moxifloxacin 400mg tablets is not recommended for use in children with a body weight below 33 kg, as recommended dose adjustments cannot be made.

Method of administration
Moxifloxacin 400mg tablets may be taken without regard to food.

Renal impairment:
No adjustment of dosage is required in patients with impaired renal function or in patients on chronic dialysis, including haemodialysis and continuous ambulatory peritoneal dialysis (see section 5.2).

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority’s (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.
Hepatic impairment:
No dosage adjustment is recommended in hepatic insufficiency (see also section 4.4).

Elderly
No dosage adjustment is required in the elderly.

4.3 Contraindications
Moxifloxacin 400mg tablets is contraindicated in:
- Patients with hypersensitivity to moxifloxacin, other quinolones or to any of the excipients.
- Patients with a history of tendon disease/disorder related to quinolone treatment.

Both in preclinical investigations and in humans, changes in cardiac electrophysiology have been observed following exposure to moxifloxacin, in the form of QT prolongation. Moxifloxacin is therefore contraindicated in patients with:
- Congenital or documented acquired QT prolongation
- Electrolyte disturbances, particularly in uncorrected hypokalaemia
- Clinically relevant bradycardia
- Clinically relevant heart failure with reduced left-ventricular ejection fraction
- Previous history of symptomatic arrhythmias

Moxifloxacin 400mg tablets should not be used concurrently with other drugs that prolong the QT interval (see also section 4.5).

4.4 Special warnings and precautions for use
Prolongation of QTc interval and potentially QTc-prolongation-related clinical conditions
Moxifloxacin has been shown to prolong the QTc interval on the electrocardiogram in some patients. In the analysis of ECGs obtained in the clinical trial program, QTc prolongation with moxifloxacin was 6 msec ± 26 msec, 1.4% compared to baseline. As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

Medication that can reduce potassium levels should be used with caution in patients receiving moxifloxacin (see also section 4.3). Moxifloxacin should be used with caution in patients who are taking medications associated with clinically significant bradycardia (see also section 4.3).

Moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as acute myocardial ischaemia or QT prolongation as this may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest (see also section 4.3). The magnitude of QT prolongation may increase with increasing concentrations of the drug. Therefore, the recommended dose should not be exceeded.

If signs or symptoms of cardiac arrhythmia occur during treatment with moxifloxacin, treatment should be stopped and an ECG should be performed.

Hypersensitivity / allergic reactions
Hypersensitivity and allergic reactions have been reported for fluoroquinolones including moxifloxacin after first administration. Anaphylactic reactions can progress to a life-threatening shock, even after the first administration. In these cases moxifloxacin should be discontinued and suitable treatment (e.g. treatment for shock) initiated.

Severe liver reactions
Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with moxifloxacin (see section 4.8). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of fulminant hepatic disease develop such as rapidly
developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy.

Liver function tests/investigations should be performed in cases where indications of liver dysfunction occur.

**Serious bullous skin reactions**
Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see section 4.8). Patients should be advised to contact their doctor or health care provider immediately prior to continuing treatment if skin and/or mucosal reactions occur.

**Prevention of photosensitivity reactions**
Quinolones have been shown to cause photosensitivity reactions in patients. Patients should be advised to avoid exposure to either UV irradiation or extensive and/or strong sunlight during treatment with moxifloxacin.

**Psychiatric reactions**
Psychiatric reactions may occur even after the first administration of quinolones, including moxifloxacin. In very rare cases depression or psychotic reactions have progressed to suicidal thoughts and self-endangering behaviour such as suicide attempts (see section 4.8). In the event that the patient develops these reactions, moxifloxacin should be discontinued and appropriate measures instituted. Caution is recommended if moxifloxacin is to be used in psychotic patients or in patients with history of psychiatric disease.

**Tendon rupture, tendon inflammation**
Tendon inflammation and rupture may occur with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids. At the first sign of pain or inflammation, patients should discontinue treatment with moxifloxacin, rest the affected limb(s) and consult their doctor or health care provider immediately in order to initiate appropriate treatment (e.g. immobilisation) for the affected tendon. Tendon inflammation and rupture may occur even up to several months after discontinuing quinolone therapy including moxifloxacin.

**Vision disorders**
If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see sections 4.7 and 4.8).

**Antibiotic-associated diarrhoea including colitis**
Antibiotic-associated diarrhoea (AAD) and antibiotic-associated colitis (AAC), including pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea, has been reported in association with the use of broad spectrum antibiotics including moxifloxacin and may range in severity from mild diarrhoea to fatal colitis. Therefore it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of moxifloxacin. If AAD or AAC is suspected or confirmed, ongoing treatment with antibacterial agents, including moxifloxacin, should be discontinued and adequate therapeutic measures should be initiated immediately. Furthermore, appropriate infection control measures should be undertaken to reduce the risk of transmission. Drugs inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.

**Peripheral neuropathy**
Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones. Patients under treatment with moxifloxacin should be advised to inform their doctor or health care provider prior to
continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop (see section 4.8).
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, moxifloxacin 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. Also, Moxifloxacin 400mg tablets is unsuitable for children and adolescents with a body weight <33 kg as the recommended dose adjustments cannot be made.

Patients with pre-existing impaired liver function
No dosage adjustment is recommended for mild, moderate, or severe hepatic insufficiency. There is insufficient experience in the clinical use of moxifloxacin in patients with impaired liver function. However, due to metabolic disturbances associated with hepatic insufficiency, which may lead to QT prolongation, moxifloxacin should be used with caution in these patients.

Patients with pre-existing renal disorders
Elderly patients with renal disorders should use moxifloxacin with caution if they are unable to maintain adequate fluid intake, because dehydration may increase the risk of renal failure.

Patients predisposed to seizures
Quinolones are known to trigger seizures. They should be used with caution in patients with CNS disorders or in the presence of other risk factors which may predispose to seizures or lower the seizure threshold. In case of seizures, treatment with moxifloxacin should be discontinued and appropriate measures instituted.

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

Patients with glucose-6-phosphate dehydrogenase deficiency
Patients with a family history of, or actual glucose-6-phosphate dehydrogenase deficiency are prone to haemolytic reactions when treated with quinolones. Therefore, moxifloxacin should be used with caution in these patients.

Patients with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption
Moxifloxacin 400mg 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

Cytochrome P450 mediated interactions
In vitro studies with cytochrome P450 isoenzymes (CYP) indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2, suggesting that moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes. Also, CYP450 isoenzymes are not known to be involved in the metabolism of moxifloxacin. Considering these results, metabolic interactions via cytochrome P450 enzymes are unlikely.

Clinical studies have shown that there are no interactions following concomitant administration of moxifloxacin with: ranitidine, probenecid, oral contraceptives, calcium supplements, morphine administered parenterally, theophylline, cyclosporine or itraconazole.
Rifampicin
When co-administered with multiple doses of rifampicin, moxifloxacin AUC decreases by approximately 30%. The clinical consequences of this are unknown, and no dose adjustment is recommended on co-administration.

Rifapentine
When co-administered with multiple doses of rifapentine, Moxifloxacin AUC decreased by 17%. The clinical consequences of this are unknown, and no dose adjustment is recommended on co-administration.

Rifabutin
No data are available on the effect of co-administration on the exposure to moxifloxacin and rifabutin.

QT-prolonging agents
An additive effect on QT interval prolongation of moxifloxacin and other agents that prolong the QT interval cannot be excluded. This effect might lead to an increased risk of ventricular arrhythmias, notably torsade de pointes. Therefore moxifloxacin is contraindicated in patients treated with any of the following drugs (see also section 4.3):
- antiarrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide),
- antiarrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide),
- neuroleptics (e.g. phenothiazines, pimozide, sertrindole, haloperidol, sultopride),
- tricyclic antidepressive agents,
- certain antimicrobials (sparfloxacin, erythromycin IV, pentamidine, antimalarials, particularly halofantrine),
- certain antihistamminics (terfenadine, astemizole, mizolastine),
- others (e.g., cisapride, bepridil).

Bivalent and trivalent cations
Chelating agents such as iron, aluminium and magnesium may inhibit the absorption of moxifloxacin. Concomitant administration or administration of agents containing these cations in temporal proximity to the intake of moxifloxacin may decrease moxifloxacin exposure by 25-60%. An interval of at least 6 hours should be left between administration of agents containing bivalent or trivalent cations (e.g. antacids containing magnesium or aluminium, didanosine tablets, sucralfate and agents containing iron or zinc) and administration of moxifloxacin.

Calcium does not affect moxifloxacin exposure, and supplements may be taken concomitantly with moxifloxacin.

Changes in INR
A large number of cases showing an increase in oral anticoagulant activity have been reported in patients receiving antibiotics, especially fluoroquinolones, macrolides, tetracyclines, cotrimoxazole and some cephalosporins. It is difficult to evaluate whether the infection or the antibiotic therapy cause the INR (international normalised ratio) disorder. A precautionary measure would be to more frequently monitor the INR in patients on warfarin or any other anticoagulants.

Interaction with food
Moxifloxacin has no clinically relevant interaction with food including dairy products.

4.6 Pregnancy and lactation
Women of childbearing potential:
Pregnancy should be avoided in women treated with moxifloxacin. Adequate contraceptive measures should be taken.
Pregnancy
The safety of moxifloxacin in human pregnancy has not been investigated. Moxifloxacin should only be used in pregnancy if the benefit is considered to outweigh the risks, and there are no available treatment alternatives. Reversible joint injuries are described in children receiving some quinolones; however this effect has not been reported as occurring on exposed foetuses. Animal studies have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Lactation
The use of moxifloxacin during breast-feeding is contraindicated. As with other quinolones, moxifloxacin has been shown to cause lesions in the cartilage of the weight bearing joints of immature animals. Preclinical data indicate that moxifloxacin passes into breast milk.

Fertility
No specific studies with moxifloxacin in humans have been conducted to evaluate effects on fertility. Animal studies do not indicate impairment of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines
No studies on the effects of moxifloxacin on the ability to drive and use machines have been performed. However, fluoroquinolones including moxifloxacin may cause impairment of the patient's ability to drive or operate machinery due to CNS reactions (e.g. dizziness; acute, transient loss of vision) or acute and short lasting loss of consciousness (syncope, see section 4.8). Patients should be advised to see how they react to moxifloxacin before driving or operating machinery.

4.8 Undesirable effects
Adverse reactions based on clinical trials with moxifloxacin 400 mg (oral and sequential therapy) sorted by frequencies are listed below. Of note, the majority of available safety data on moxifloxacin has been generated in patients with other conditions than tuberculosis in studies of less than three weeks duration.

Adverse events considered at least possibly related to moxifloxacin treatment are listed below by body system, organ class and frequency. In some cases, no frequency data can be given. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100, <1/10), uncommon (≥ 1/1000, <1/100), rare (≥ 1/10000, <1/1000), very rare (<1/10000), ‘not known’.

Infections and infestations:
Common: superinfection due to resistant bacteria or fungi, e.g. oral and vaginal candidiasis.

Blood and lymphatic system disorders:
Uncommon: anaemia, leucopenia, neutropenia, thrombocytopenia, thrombocythaemia, eosinophilia, prothrombin time prolonged /INR increased.
Very rare: Prothrombin level increased /INR decreased, agranulocytosis.

Immune system disorders:
Uncommon: allergic reaction (see section 4.4.)
Rare: anaphylaxis. angioedema.

Metabolism and nutrition disorders:
Uncommon: hyperlipaemia
Rare: hyperglycaemia, hyperuricaemia.
Psychiatric disorders:
Uncommon: anxiety reactions, psychomotor hyperactivity/agitation
Rare: emotional lability, depression, hallucination
Very rare: depersonalisation, psychosis.

Nervous system disorders:
Common: headache, dizziness
Uncommon: paraesthesia, taste disorders, confusion and disorientation, insomnia, somnolence, tremor, vertigo
Rare: hypoesthesia, smell disorders, abnormal dreams, disturbed coordination (including gait disturbances, especially due to dizziness or vertigo), seizures including grand mal convulsions (see section 4.4), disturbed attention, speech disorders, amnesia
Very rare: hyperaesthesia.

Eye disorders:
Uncommon: visual disturbances including diplopia and blurred vision (especially in the course of CNS reactions, see section 4.4)
Very rare: transient loss of vision (especially in the course of CNS reactions, see section 4.4).

Ear and labyrinth disorders:
Rare: tinnitus, hearing impairment including deafness (usually reversible).

Cardiac disorders:
Uncommon: QT prolongation (see section 4.3 and 4.4), palpitations, tachycardia, atrial fibrillation, angina pectoris
Rare: ventricular tachyarrhythmias, syncope
Very rare: torsade de pointes (see section 4.4), cardiac arrest (see section 4.4),

Vascular disorders:
Uncommon: vasodilatation
Rare: hypertension, hypotension.

Respiratory, Thoracic and Mediastinal Disorders:
Uncommon: dyspnea (including asthmatic conditions).

Gastrointestinal disorders:
Common: Nausea, vomiting, abdominal pain, diarrhoea
Uncommon: Anorexia, constipation, dyspepsia, flatulence, gastritis, increased amylase
Rare: Dysphagia, stomatitis, antibiotic associated colitis (including pseudomembranous colitis, in very rare cases associated with life-threatening complications, see section 4.4).

Hepatobiliary disorders:
Common: increase in transaminases
Uncommon: increased bilirubin, increased gamma-glutamyl-transferase, increase in blood alkaline phosphatase.
Rare: jaundice, hepatitis (predominantly cholestatic)
Very rare: fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases, see section 4.4).

Skin and subcutaneous tissue disorders:
Uncommon: pruritus, rash, urticarial, dry skin
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Very rare: bullous skin reactions, including Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life-threatening, see section 4.4).

Musculoskeletal, Connective Tissue and Bone Disorders:

Uncommon: arthralgia, myalgia

Rare: tendinitis (see section 4.4), muscle cramp, muscle twitching, muscle weakness

Very rare: tendon rupture (see section 4.4), arthritis, muscle rigidity, exacerbation of symptoms of myasthenia gravis (see section 4.4).

Renal and Urinary Disorders

Uncommon: dehydration

Rare: renal impairment (incl. increase in BUN and creatinine), renal failure (see section 4.4).

General Disorders and Administration Site Conditions:

Uncommon: asthenia, fatigue, sweating.

Rare: oedema.

There have been very rare cases of the following side effects reported following treatment with other fluoroquinolones, which might possibly also occur during treatment with moxifloxacin: hypernatraemia, hypercalcaemia, haemolytic anaemia, rhabdomyolysis, photosensitivity reactions, peripheral neuropathy (see section 4.4).

4.9 Overdose

No specific countermeasures after accidental overdose are recommended. General symptomatic therapy should be initiated. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Concomitant administration of charcoal with a dose of 400 mg oral moxifloxacin will reduce systemic availability of the drug by more than 80%. The use of charcoal early during absorption may be useful to prevent excessive increase in the systemic exposure to moxifloxacin in cases of oral overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones, ATC code: J01 MA14

Mechanism of action

Moxifloxacin 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 moxifloxacin against M. Tuberculosis results from the inhibition of the DNA gyrase, encoded by the gyrA and gyrB genes.

The wild-type moxifloxacin MIC distribution for clinical isolates of M. Tuberculosis has been reported by different investigators to range between 0.03-1 mg/L. 0.5 mg/L has been suggested as a susceptibility breakpoint. 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 experience

In a randomised controlled trial in smear positive patients with drug susceptible pulmonary tuberculosis, moxifloxacin 400 mg once daily or isoniazid, in combination with rifampicin, pyrazinamide and ethambutol, yielded 60% (99/164) and 55% (90/164) patients with negative cultures at week 8 for the moxifloxacin and the isoniazid group, respectively (p=0.37). In another randomised trial, where moxifloxacin or ethambutol was used in combination with rifampicin, isoniazid and...
pyrazinamide, also in smear positive patients with drug susceptible pulmonary tuberculosis, the 8 week culture conversion to negative rate was 80% (59/74) in the moxifloxacin group compared with 63% 45/72 in the ethambutol group (p=0.03).

There are no randomised controlled trials of moxifloxacin in MDR-TB, and the optimal dose has not been formally established.

5.2 Pharmacokinetic properties

Absorption and Bioavailability
Following oral administration moxifloxacin is rapidly and almost completely absorbed. The absolute bioavailability amounts to approximately 90%.

Following single dose administration of Moxifloxacin 400mg tablets in healthy volunteers, the mean (√± SD) moxifloxacin Cmax value was 2.123 µg/ml (± 0.679) and the corresponding value for AUC was 25.7 µg/ml (± 6.7). The mean (√± SD) moxifloxacin Tmax value was 2.30 (± 1.09) hours.

Pharmacokinetics are linear in the range of 50 - 800 mg single dose and up to 600 mg once daily dosing over 10 days. Peak and trough plasma concentrations at steady-state (400 mg once daily) were 3.2 and 0.6 mg/l, respectively.

Distribution
The steady-state volume of distribution (Vss) is approximately 2 l/kg. In vitro and ex vivo experiments showed a protein binding of approximately 40 - 42% independent of the concentration of the drug. Moxifloxacin is mainly bound to serum albumin.

Metabolism
Moxifloxacin undergoes Phase II biotransformation and is excreted via renal and biliary/faecal pathways as unchanged drug as well as in the form of a sulpho-compound (M1) and a glucuronide (M2). M1 and M2 are the only metabolites relevant in humans, both are microbiologically inactive.

Elimination
Moxifloxacin is eliminated from plasma with a mean terminal half life of approximately 12 hours. The mean apparent total body clearance following a 400 mg dose ranges from 179 to 246 ml/min. Renal clearance amounted to about 24 - 53 ml/min suggesting partial tubular reabsorption of the drug from the kidneys.

Special populations
The pharmacokinetic properties of moxifloxacin are not significantly different in patients with renal impairment (including creatinine clearance≥ 20 ml/min/1.73 m²). As renal function decreases, concentrations of the M2 metabolite (glucuronide) increase by up to a factor of 2.5 (with a creatinine clearance of < 30 ml/min/1.73 m²).

On the basis of the pharmacokinetic studies carried out so far in patients with liver failure (Child Pugh A, B), it is not possible to determine whether there are any differences compared with healthy volunteers. Impaired liver function was associated with higher exposure to M1 in plasma, whereas exposure to parent drug was comparable to exposure in healthy volunteers.
5.3 Preclinical safety data

Effects on the haematopoetic system (slight decreases in the number of erythrocytes and platelets) were seen in rats and monkeys. As with other quinolones, hepatotoxicity (elevated liver enzymes and vacuolar degeneration) was seen in rats, monkeys and dogs. In monkeys, CNS toxicity (convulsions) occurred. These effects were seen only after treatment with high doses of moxifloxacin or after prolonged treatment. Moxifloxacin, like other quinolones, was genotoxic in in vitro tests using bacteria or mammalian cells. Since these effects can be explained by an interaction with the gyrase in bacteria and - at higher concentrations - by an interaction with the topoisomerase II in mammalian cells, a threshold concentration for genotoxicity can be assumed. In in vivo tests, no evidence of genotoxicity was found despite the fact that very high moxifloxacin doses were used. Thus, a sufficient margin of safety to the therapeutic dose in man can be provided. Moxifloxacin was non-carcinogenic in an initiation-promotion study in rats.

Many quinolones are photoreactive and can induce phototoxic, photomutagenic and photocarcinogenic effects. In contrast, moxifloxacin was proven to be devoid of phototoxic and photogenotoxic properties when tested in a comprehensive programme of in vitro and in vivo studies. Under the same conditions other quinolones induced effects.

At high concentrations, moxifloxacin is an inhibitor of the rapid component of the delayed rectifier potassium current of the heart and may thus cause prolongations of the QT interval. Toxicological studies performed in dogs using oral doses of ≥90 mg/kg leading to plasma concentrations ≥16 mg/l caused QT prolongations, but no arrhythmias. Only after very high cumulative intravenous administration of more than 50-fold the human dose (> 300 mg/kg), leading to plasma concentrations of ≥200 mg/l (more than 40-fold the therapeutic level), reversible, non-fatal ventricular arrhythmias were seen.

Quinolones are known to cause lesions in the cartilage of the major diarthrodial joints in immature animals. The lowest oral dose of moxifloxacin causing joint toxicity in juvenile dogs was four times the maximum recommended therapeutic dose of 400 mg (assuming a 50 kg bodyweight) on a mg/kg basis, with plasma concentrations two to three times higher than those at the maximum therapeutic dose.

Toxicity tests in rats and monkeys (repeated dosing up to six months) revealed no indication regarding an oculotoxic risk. In dogs, high oral doses (≥ 60 mg/kg) leading to plasma concentrations ≥20 mg/l caused changes in the electroretinogram and in isolated cases an atrophy of the retina.

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Studies in rats (p.o. and i.v.) and monkeys (p.o.) did not show evidence of teratogenicity or impairment of fertility following administration of moxifloxacin. A slightly increased incidence of vertebral and rib malformations was observed in foetuses of rabbits but only at a dose (20 mg/kg i.v.) which was associated with severe maternal toxicity. There was an increase in the incidence of abortions in monkeys and rabbits at human therapeutic plasma concentrations. In rats, decreased foetal weights, an increased prenatal loss, a slightly increased duration of pregnancy and an increased spontaneous activity of some male and female offspring was observed at doses which were 63 times the maximum recommended dose on a mg/kg basis with plasma concentrations in the range of the human therapeutic dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Core tablet: Croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and microcrystalline cellulose.
Film coat: Hydroxypropyl methylcellulose, iron oxide red, polyethylene glycol, purified talc and titanium dioxide.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
36 months

6.4 Special precautions for storage
Do not store above 30°C. Store in a dry place. Protect from Light.

6.5 Nature and contents of container
Alu-Alu blister pack made of blister aluminium foil and cold blister foil. Each blister pack contains 5 tablets and 1 or 20 such blister packs are packed in a carton along with the leaflet.
Alu-Alu strip pack made of plain and printed aluminium foil. Each strip pack contains 5 tablets and 1 or 20 such strip packs are packed in a carton along with the leaflet.
Alu-Alu blister pack made of blister aluminium foil and cold blister foil. Each blister pack contains 7 tablets and 10 such blister packs are packed in a carton along with the leaflet.
Alu-Alu strip pack made of plain and printed aluminium foil. Each strip pack contains 7 tablets and 10 such strip packs are packed in a carton along with the leaflet.
Alu-Alu blister pack made of blister aluminium foil and cold blister foil. Each blister pack contains 10 tablets and 10 such blister packs are packed in a carton along with the leaflet.
Alu-Alu strip pack made of plain and printed aluminium foil. Each strip pack contains 10 tablets and 10 such strip packs are packed in a carton along with the leaflet.

6.6 Special precautions for disposal
No special requirements

7. SUPPLIER
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8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)
TB230

9. DATE OF FIRST PREQUALIFICATION/ LAST RENEWAL
16 November 2012

10. DATE OF REVISION OF THE TEXT

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