



National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

MICRO LABS LIMITED, INDIA

SUMMARY OF PRODUCT CHARACTERISTICS

ORNIDAZOLE 500mg & OFLOXACIN 200mg TABLET (ORNILOX)



1. NAME OF THE MEDICINAL PRODUCT

ORNILOX

2. QUALITY AND QUANTITATIVE COMPOSITION

Each film-coated Tablet contains:

Ornidazole500mg

Ofloxacin USP200mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Orange coloured caplet shaped film-coated tablets with a "MICRO" engraved on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

Ornidazole & Ofloxacin is indicated for empirical treatment of mixed aerobic-anaerobic infections commonly seen in clinical practice e.g. intra-abdominal infection, gynecological and pelvic infections, foot ulcers especially in diabetes, lung abscess, infections in immune-compromised patients etc.

4.2 Posology and method of administration:

The usual adult dose is one tablet of Orniox tablet twice a day. The doses may be increased in severe infections. The duration of treatment depends upon the type and severity of infection. These recommendations apply to patients with normal renal function (i.e., Creatinine clearance > 50 ml/min).

Adults: 1 tablet twice daily for 5 to 10 days.

4.3 Contraindications:

Ofloxacin should not be used in patients with known hypersensitivity to 4quinoloneantibacterials

Or any of the tablet excipients

- Ofloxacin should not be used in patients with a past history of tendinitis.
- Ofloxacin, like other 4-quinolones, is contra-indicated in patients with a history of epilepsy or with a lowered seizure threshold.



- Ofloxacin is contra-indicated in children or growing adolescents, and in pregnant or breastfeeding women, since animal experiments do not entirely exclude the risk of damage to the cartilage of joints in the growing subject.
- Patients with actual defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents.
- Patients with known hypersensitivity to ornidazole or any component of this formulation or active renal disease or hepatic cirrhosis.

4.4 Special warning and precautions:

Methicillin-resistant *S. aureus* are very likely to possess co-resistance to fluoroquinolones, including ofloxacin. Therefore ofloxacin is not recommended for the treatment of known or suspected MRSA infections unless laboratory results have confirmed susceptibility of the organism to ofloxacin (and commonly recommended antibacterial agents for the treatment of MRSA-infections are considered inappropriate).

Escherichia coli infection

Resistance to fluoroquinolones of *E. coli* – the most common pathogen involved in urinary tract infections – varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in *E. coli* to fluoroquinolones. Ofloxacin is not the drug of first choice for pneumonia caused by Pneumococci or Mycoplasma or infection caused by β -haemolytic Streptococci.

Neisseria gonorrhoeae infections

Due to increase in resistance to *N. gonorrhoeae*, ofloxacin should not be used as empirical treatment option in suspected gonococcal infection (urethral gonococcal infection, pelvic inflammatory disease and Epididymo-orchitis), unless the pathogen has been identified and confirmed as susceptible to ofloxacin. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Pelvic inflammatory disease

For pelvic inflammatory disease, ofloxacin should only be considered in combination with anaerobe coverage.

Hypersensitivity and allergic reactions

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



Severe bullous reactions

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

Clostridium difficile-associated disease

Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with ofloxacin (including several weeks after treatment), may be symptomatic of pseudo-membranous colitis (CDAD). CDAD may range in severity from mild to life threatening, the most severe form which is pseudomembranous colitis. It is therefore important to consider this diagnosis in patients who develop serious diarrhoea during or after treatment with ofloxacin. If pseudo-membranous colitis is suspected, ofloxacin must be stopped immediately.

Appropriate specific antibiotic therapy must be started without delay (e.g. oral vancomycin, oral teicoplanin or metronidazole). Products inhibiting the peristalsis are contraindicated in this clinical situation

Patients predisposed to seizures

Quinolones may lower the seizure threshold and may trigger seizures. Ofloxacin is contraindicated in patients with a history of epilepsy and, as with other quinolones, ofloxacin should be used with extreme caution in patients predisposed to seizures.

Such patients may be 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.

In case of convulsive seizures, treatment with ofloxacin should be discontinued

Tendinitis

Tendinitis, rarely observed with quinolones, may occasionally lead to rupture involving Achilles tendon in particular. Tendinitis and tendon rupture, sometimes bilateral, may occur within 48 hours of starting treatment with ofloxacin and have been reported up to several months after discontinuation of. The risk of tendinitis and tendon rupture is increased in patients aged over 60 years and in patients using corticosteroids. Furthermore, as transplanted patients are at increased risk of tendinitis, caution is recommended when fluoroquinolones are used in this population. The daily dose should be adjusted in elderly patients based on creatinine clearance. Close monitoring of these patients is therefore necessary if they are prescribed ofloxacin. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with ofloxacin must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.



Patients with renal impairment

Since ofloxacin is mainly excreted by the kidneys, the dose of ofloxacin should be adjusted in patients with renal impairment

QT interval prolongation

Very rare cases of QT interval prolongation have been reported in patients taking fluoroquinolones. Caution should be taken when using fluoroquinolones, including ofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:

- Congenital long QT syndrome
- Concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
- Uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- Cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
- Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including Ofloxacin, in these populations.

Patients with history of psychotic disorder

Psychotic reactions have been reported in patients receiving fluoroquinolones. In some cases these have progressed to suicidal thoughts or self-endangering behaviour including suicide attempt, sometimes after a single dose. In the event that a patient develops these reactions, ofloxacin should be discontinued and appropriate measures instituted.

Ofloxacin should be used with caution in patients with a history of psychotic disorder or in patients with psychiatric disease.

Patients with impaired liver function

Ofloxacin should be used with caution in patients with impaired liver function, as liver damage may occur. Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with fluoroquinolones. 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, pruritis or tender abdomen.

Patients treated with vitamin K antagonists

Due to possible increase in coagulation tests (PT/INR) and/or bleeding in patients treated with fluoroquinolones, including ofloxacin, in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomitantly

Myasthenia gravis

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

Prevention of photosensitisation

Photosensitisation has been reported with ofloxacin. 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

Super infection

As with other antibiotics, the use of ofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If secondary infection occurs during therapy, appropriate measures should be taken.

Peripheral neuropathy

Sensory or sensorimotor peripheral neuropathy has been reported in patients receiving fluoroquinolones, including ofloxacin, which can be rapid in its onset. Ofloxacin should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both Hyperglycaemia and hypoglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In these diabetic patients, careful monitoring of blood glucose is recommended.

Patients with glucose-6-phosphate-dehydrogenase deficiency

Patients with latent or diagnosed glucose-6-phosphate-dehydrogenase deficiency may be predisposed to haemolytic reactions if they are treated with quinolones. Therefore, if ofloxacin has to be used in these patients, potential occurrence of haemolysis should be monitored.

Vision disorders

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

Interference with laboratory tests

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 more specific method.



Very rarely, patients treated with fluoroquinolone or quinolone antibiotics have suffered long-lasting and disabling side effects, mainly involving muscles, tendons and bones and the nervous system. Fluoroquinolone and quinolone antibiotics should not be used

- To treat infections that might get better without treatment or are not severe (such as throat infections);
- For preventing traveller's diarrhoea or recurring lower urinary tract infections (urine infections that do not extend beyond the bladder);
- To treat patients who have previously had serious side effects with a fluoroquinolone or quinolone antibiotic;
- To treat mild or moderately severe infections unless other antibacterial medicines commonly recommended for these infections cannot be used;
- Be used with caution especially for the elderly, patients with kidney problems, patients who have had organ transplantation or those who are being treated with a systemic corticosteroid. These patients are at higher risk of tendon injury caused by fluoroquinolone and quinolone antibiotics.

Ornidazole

Regular laboratory tests and clinical control are indicated in case of use of high Ornidazole doses or if duration of therapy exceeds 10 days.

Blood disorders: Leukocyte counts should be checked before and after start of therapy (especially in repeat therapy), in patients with history of blood disorders. CNS: Severe diseases of central and peripheral nervous system may get aggravated on Ornidazole therapy.

Treatment should be discontinued in case of onset of peripheral neuropathy, ataxia, vertigo or confusion.

Candidiasis: Ornidazole therapy may aggravate existing candidiasis. Necessary precautions should be taken.

4.5 Interactions with Other Medicaments

Ofloxacin

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 anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)

Antacids, Sucralfate, Metal Cations



Co-administered magnesium/aluminium antacids, sucralfate, zinc or iron preparations can reduce absorption. Therefore, ofloxacin should be taken 2 hours before such preparations.

Prolongation of bleeding time has been reported during concomitant administration of Tarivid and anticoagulants.

Theophylline, fenbufen or similar non-steroidal antiinflammatory drugs

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, nonsteroidal antiinflammatory drugs, or other agents, which lower the seizure threshold.

In case of convulsive seizures, treatment with ofloxacin should be discontinued.

Glibenclamide

Ofloxacin may cause a slight increase in serum concentrations of glibenclamide administered concurrently; patients treated with this combination should be closely monitored.

Probenecid, cimetidine, furosemide and methotrexate

Probenecid decreased the total clearance of ofloxacin by 24%, and increased AUC by 16%. The proposed mechanism is a competition or inhibition for active transport at the renal tubular excretion. Caution should be exercised when ofloxacin is coadministered with drugs that affect the tubular renal secretion such as Probenecid, cimetidine, furosemide and methotrexate.

Vitamin K antagonists

Increased coagulation tests (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) Coagulation tests should be monitored in patients treated with vitamin K antagonists because of a possible increase in the effect of coumarin derivatives.

Ornidazole

Alcohol intolerance: Unlike other nitro-imidazole, Ornidazole does not inhibit enzyme aldehyde dehydrogenase. No disulfiram like reaction has been reported on consumption of alcohol. However, as is the case with all imidazole, this drug should be avoided in concomitance with alcohol usage No clinically relevant interactions were seen with food and no interaction was found between ofloxacin and theophylline.



4.6 Fertility, pregnancy and lactation

Ofloxacin

Based on a limited amount of human data, the use of fluoroquinolones in the first trimester of pregnancy has not been associated with an increased risk of major malformations or other adverse effects on pregnancy outcome. Animal studies have shown damage to the joint cartilage in immature animals but no teratogenic effects. Therefore Ofloxacin should not be used during pregnancy.

Ofloxacin is excreted into human breast milk in small amounts. Because of the potential for arthropathy and other serious toxicity in the nursing infant, breast feeding should be discontinued during treatment with Ofloxacin.

Ornidazole

No controlled studies of effect of the drug on pregnant women are available. Ornidazole should be prescribed to pregnant and nursing women only if the potential benefit to the mother outweighs potential risk to the foetus/ neonate. Lithium therapy: 5-nitroimidazoles (mainly metronidazole) have been found to decrease renal elimination of lithium. So, in patients undergoing concurrent lithium therapy, plasma lithium concentrations as well as creatinine and electrolyte concentrations should be monitored. It should be used with caution in conditions where the individual drugs have been used with precautionary approach.

4.7 Effects on ability to drive and use machine:

Ofloxacin

Since there have been occasional reports of somnolence, impairment of skills, dizziness and visual disturbances, patients should know how they react to ofloxacin before they drive or operate machinery. These effects may be enhanced by alcohol.

Ornidazole

Somnolence, dizziness, tremor, rigidity, poor coordination, seizures, vertigo or temporary loss of consciousness may occur in patients receiving Ornidazole. If they occur, such effects may affect tasks requiring alertness, including the patient's ability to drive and operate machinery.

4.8 Undesirable effects:

Ofloxacin



System organ class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (< 1/10,000)	Not known (cannot be estimated from available data)*
Infections and infestations		Fungal infection, Pathogen resistance			
Blood and the lymphatic system disorders				Anaemia Haemolytic anaemia, Leukopenia, Eosinophilia, Thrombocytopenia	Agranulocytosis Bone marrow failure
Immune system disorders			Anaphylactic reaction*, Anaphylactoid reaction*, Angioedema*	Anaphylactic shock*, Anaphylactoid shock*	
Metabolism and Nutrition disorders			Anorexia		Hypoglycaemia in diabetics treated with hypoglycaemic agents Hyperglycaemia Hypoglycaemic coma
Psychiatric disorders		Agitation, Sleep disorder, Insomnia	Psychotic disorder (for e.g. hallucination), Anxiety, Confusional		Psychotic disorder and depression with self-endangering behaviour including suicidal



			state, Nightmares, Depression		ideation or suicide attempt Nervousness
Nervous system disorders		Dizziness, Headache	Somnolence, Paraesthesia, Dysgeusia, Parosmia	Peripheral sensory neuropathy* Peripheral sensory motor neuropathy* Convulsion*, Extra-pyramidal symptoms or other disorders of muscular coordination	Tremor Dyskinesia Ageusia Syncope
Eye disorders		Eye irritation	Visual disturbance		Uveitis
Ear and labyrinth disorders		Vertigo		Tinnitus, Hearing loss	Hearing impaired
Cardiac disorders			Tachycardia		Ventricular arrhythmias, torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged
Vascular disorders	<i>applies only to the solution for infusion:</i> Phlebitis		Hypotension		<i>applies only to the solution for infusion:</i> During infusion of ofloxacin,



					tachycardia and hypotension may occur. Such a decrease in blood pressure may, in very rare cases, be severe.
Respiratory, thoracic and mediastinal disorders		Cough, Nasopharyngitis	Dyspnoea, Bronchospasm		Allergic pneumonitis, Severe dyspnoea
Gastro- intestinal disorders		Abdominal pain, Diarrhoea, Nausea, Vomiting	Enterocolitis, sometimes haemorrhagic	Pseudomembranous colitis* Jaundice cholestatic	Dyspepsia Flatulence Constipation Pancreatitis
Hepato-biliary disorders			Hepatic enzymes increased (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) Blood bilirubin increased		Hepatitis, which may be severe*; Severe liver injury, including cases with acute liver failure, sometimes fatal, have been reported with ofloxacin, primarily in patients with underlying liver disorders
Skin and subcutaneous		Pruritus, Rash	Urticaria, Hot flushes,	Erythema multiforme, Toxic epidermal necrolysis, Photo-	Stevens-Johnson syndrome; Acute



tissue disorders			Hyperhidrosis Pustular rash	sensitivity reaction*, Drug eruption Vascular purpura, Vasculitis, which can lead in exceptional cases to skin necrosis	generalized exanthemous pustulosis; drug rash Stomatitis; Exfoliative dermatitis
Musculoskeletal and Connective tissue disorders			Tendinitis	Arthralgia, Myalgia, Tendon rupture (e.g. Achilles tendon) which may occur within 48 hours of treatment start and may be bilateral.	Rhabdomyolysis and/or Myopathy, Muscular weakness Muscle tear, muscle rupture Ligament rupture Arthritis
Renal and Urinary disorders			Serum creatinine increased	Acute renal failure	Acute interstitial nephritis
Congenital and familial/genetic disorders					Attacks of porphyria in patients with porphyria
General disorders and administration site conditions	<i>applies only to the solution for infusion:</i> Infusion site reaction (pain, reddening)				

Ornidazole

Gastrointestinal effects like nausea, vomiting, anorexia and metallic or bitter taste. CNS effects like



dizziness, vertigo and somnolence, rigidity, tremor, coordination problems, convulsions (rare), impairment of consciousness and signs of sensitive or mixed peripheral neuropathy have been observed. Blood dyscrasias like medullar aplasia and neutropenia may be encountered occasionally. Other adverse events such as fatigue, loose stools, and headache have also been reported.

4.9 Overdose:

Ofloxacin

The most important signs to be expected following acute over dosage are CNS symptoms such as confusion, dizziness, impairment of consciousness and convulsive seizures as well as gastrointestinal reactions such as nausea and mucosal erosions.

In the case of overdose steps to remove any unabsorbed Ofloxacin e.g gastric lavage, administration of adsorbents and sodium sulphate, if possible during the first 30 minutes, are recommended; antacids are recommended for protection of the gastric mucosa.

Elimination of Ofloxacin may be increased by forced diuresis.

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

Ornidazole

In cases of over dosage the symptoms mentioned under Undesirable Effects occur in more severe form. No specific antidote is known. The administration of diazepam is recommended if cramps occur.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties:

Ofloxacin

Ofloxacin is a quinolone antimicrobial agent. The mechanism of action of Ofloxacin 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.

Ofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Ofloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations. Fluoroquinolones, including Ofloxacin, differ in chemical structure and mode of action from aminoglycosides, macrolides and beta-lactam antibiotics, including penicillins. Fluoroquinolones may, therefore, be active against bacteria resistant to these antimicrobials.



Resistance to Ofloxacin due to spontaneous mutation *in vitro* is a rare occurrence (range: 10⁻⁹ to 10⁻¹¹). Although cross-resistance has been observed between Ofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to Ofloxacin.

Ofloxacin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections:

Aerobic Gram-positive Microorganisms

Staphylococcus aureus (methicillin-susceptible strains)

Streptococcus pneumoniae (penicillin-susceptible strains)

Streptococcus pyogenes

Aerobic Gram-negative Microorganisms

Citrobacter (diversus) koseri

Enterobacter aerogenes

Escherichia coli

Haemophilus influenzae

Klebsiella pneumoniae

Neisseria gonorrhoeae

Proteus mirabilis

Pseudomonas aeruginosa

As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with Ofloxacin.

Other Microorganisms

Chlamydia trachomatis

The following *in vitro* data are available, but their clinical significance is unknown. Ofloxacin exhibits *in vitro* minimum inhibitory concentrations (MIC values) of 2 mcg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of Ofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic Gram-positive Microorganisms

Staphylococcus epidermidis (methicillin-susceptible strains)

Staphylococcus saprophyticus

Streptococcus pneumoniae (penicillin-resistant strains)

Aerobic Gram-negative Microorganisms

Acinetobacter calcoaceticus

Bordetella pertussis



Citrobacter freundii

Enterobacter cloacae

Haemophilus ducreyi

Klebsiella oxytoca

Moraxella catarrhalis

Morganella morganii

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Serratia marcescens

Anaerobic Microorganisms

Clostridium perfringens

Other Microorganisms

Chlamydia pneumoniae

Gardnerella vaginalis

Legionella pneumophila

Mycoplasma hominis

Mycoplasma pneumoniae

Ureaplasma urealyticum

Ofloxacin is not active against *Treponema pallidum*.

Many strains of other streptococcal species, *Enterococcus* species, and anaerobes are resistant to Ofloxacin.

Ornidazole

After passive absorption into bacterium cell, the nitro group of Ornidazole is reduced to amine group by ferredoxin type redox system. The formation of redox intermediate intracellular metabolites is believed to be the key component of microorganism killing for Ornidazole. The mechanism of action is similar in protozoa.

Microbiology

Microbiological results indicate that the following pathogens may be regarded as sensitive: Staphylococcus aureus (including methicillin resistant staphylococci), Staphylococcus epidermidis, Neisseria species, Escherichia coli, Citrobacter, Klebsiella, Enterobacter, Hafnia, Proteus (indole negative and indole-positive strains), Haemophilus influenzae, Chlamydiae, Legionella, and Gardnerella. Variable



sensitivity is shown by Streptococci, Serratia marcescens, Pseudomonas aeruginosa and Mycoplasma. Anaerobic bacteria (e.g. Fusobacterium species, Bacteroides species, Eubacterium species, Peptococci, Peptostreptococcus) are normally resistant. Ofloxacin is not active against Treponema pallidum.

5.2 Pharmacokinetic Properties:***Ofloxacin***

Following oral administration to healthy elderly subjects (65 to 81 years of age), maximum plasma concentrations are usually achieved 1 to 3 hours after single and multiple twice-daily doses, indicating that the rate of oral absorption is unaffected by age or gender. Mean peak plasma concentrations in elderly subjects were 9 to 21% higher than those observed in younger subjects. Gender differences in the pharmacokinetic properties of elderly subjects have been observed. Peak plasma concentrations were 114% and 54% higher in elderly females compared with elderly males following single and multiple twice-daily doses. Plasma concentrations increase dose-dependently with the increase in doses after a single oral dose and at the steady state. No differences were observed in the volume of distribution values between elderly and younger subjects. As in younger subjects, elimination is mainly by renal excretion as unchanged drug in elderly subjects, although fewer drugs is recovered from renal excretion in elderly subjects. Consistent with younger subjects, less than 5% of an administered dose was recovered in the urine as the desmethyl and N-oxide metabolites in the elderly. A longer plasma half-life of approximately 6.4 to 7.4 hours was observed in elderly subjects, compared with 4 to 5 hours for young subjects. Slower elimination of Ofloxacin is observed in elderly subjects as compared with younger subjects, which may be attributable to the reduced renal function and renal clearance observed in the elderly subjects. Because Ofloxacin is known to be substantially excreted by the kidneys, and elderly patients are more likely to have decreased renal function, dosage adjustment is necessary for elderly patients with impaired renal function as recommended for all patients.

Following oral administration of recommended therapeutic doses, Ofloxacin has been detected in blister fluid, cervix, lung tissue, ovary, prostatic fluid, prostatic tissue, skin, and sputum. The mean concentration of Ofloxacin in each of these various body fluids and tissues after one or more doses was 0.8 to 1.5 times the concurrent plasma level. Inadequate data are presently available on the distribution or levels of Ofloxacin in the cerebrospinal fluid or brain tissue.

Ofloxacin has a pyridobenzoxazine ring that appears to decrease the extent of the parent compound metabolism. 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. About 4 to 8% of an Ofloxacin dose is excreted in the faeces. This indicates a small degree of biliary excretion of Ofloxacin.

The administration of Ofloxacin tablets with food does not affect the Cmax and AUC(infinity) of the drug, but the Tmax is prolonged.

Clearance of Ofloxacin is reduced in patients with impaired renal function (creatinine clearance rate ≤ 50 mL/min), and dosage adjustment is necessary.

Ornidazole

Following oral administration Ornidazole is rapidly absorbed. Mean absorption is 90%. Peak plasma concentrations are reached within 3 hours. The mean volume of distribution after intravenous administration is 1 litre per kg. Plasma protein binding of Ornidazole is about 13%. The active ingredient of Ornidazole penetrates the cerebrospinal fluid, the body fluids and the tissues very effectively. Plasma concentrations are within the range considered to be optimal for the various indications (6 to 36 mg/l).

After repeated administration of 500 mg or 1,000 mg every 12 hours to healthy volunteers, an accumulation factor of 1.5 to 2.5 was calculated.

Ornidazole is mainly metabolized to 2-hydroxymethyl and a-hydroxymethylmetabolites in the liver. Both main metabolites are less active against *Trichomonas vaginalis* and anaerobic bacteria than the unchanged Ornidazole.

The half-life is about 13 hours. While 85% of a single dose is eliminated within the first 5 days (most of this being metabolized), 4% of the dose is excreted as unaltered substance in the urine.

Patients with Hepatic Impairment

In patients with liver cirrhosis, the elimination half-life is longer (22 versus 14 hours) and clearance lower (35 versus 51 ml/min) than in healthy subjects. The dosing interval should be doubled in patients with severe hepatic impairment.

Patients with Renal Impairment

The pharmacokinetics of Ornidazole is unaltered in renal impairment. Dose adjustment is, therefore, unnecessary in patients with impaired renal function. Ornidazole is removed by haemodialysis. An additional dose of 500 mg of Ornidazole should be administered if the daily dose is 2 g/d, or an additional

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dose of 250 mg Ornidazole if the daily dose is 1 g/d, should, therefore, be administered before the start of haemodialysis.

Neonates and Children

The pharmacokinetics of Ornidazole in neonates and young children is similar to those in adults.

5.3 Preclinical safety Data:

Few studies have shown the combination of Nitroimidazoles and Quinolones to be effective clinically. This gives an indication for combining Ornidazole and ofloxacin especially in mixed infections. Ornidazole which is a new derivative of Nitroimidazoles series has a longer half-life. It is recommended to be given twice a day. Ofloxacin is also recommended twice daily. Therefore, it appears appropriate to combine Ornidazole and ofloxacin as fixed dose combinations. Moreover, FDC will provide broad spectrum of activity as individual drugs are active against both aerobic and anaerobic infection.

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Microcrystalline Cellulose, Sodium Starch Glycollate, Croscarmellose Sodium, Colloidal Anhydrous Silica, Talc, Magnesium stearate, Hypromellose, Opadry Orange II 33G53350, Lake of Quinoline Yellow .

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

2 years

6.4 Special precautions for storage:

Store below 30°C. Keep away from the reach of children

6.5 Nature and contents of container:

10 tablets are packed in Alu/Alu blister. Such one blister are packed in a carton along with a pack insert.

6.6 Special precautions for disposal

No special requirements

7. Marketing Authorization Holder:

MICRO LABS LIMITED

31, Race course road

Bangalore-560001

INDIA

8. Marketing Authorization Numbers

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9. Date of first authorization

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MICRO LABS LIMITED, INDIA

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10. Date of revision of the text

Feb 2021