Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
FLOXYL-O TABLETS

2. Qualitative and quantitative composition
Each coated tablet contains,
Ofloxacin USP.....200 mg
Ornidazole IH .....500 mg

For the full list of excipients, see section 6.1

3. Pharmaceutical form
Film-coated tablets.
Description- Orange coloured, caplet shaped, biconvex film coated tablet, plain on both sides.

4. Clinical particulars
4.1 Therapeutic indications
Ofloxacin and Ornidazole combination
Ofloxacin and Ornidazole Tablet are indicated for the treatment of diarrhoea of mixed infection in adults only.
Ofloxacin and Ornidazole Tablet is used to treat infections caused by bacteria requiring and not requiring oxygen for growth. These infections include diarrhoea, stomach infection, disorders of the female reproductive system and pelvic infections.
It also used to treat foot ulcers especially in patients with diabetes, lung infection, and patients with a weak immune system. This medicine works by killing bacteria that cause infections.

Ofloxacin
The following indications are restricted to adults.
Ofloxacin is suitable for treatment of the following bacterial infections if these are caused by pathogens sensitive to ofloxacin.
• Lower respiratory tract infections including pneumonia, bronchitits and acute exacerbations of chronic bronchitis caused by gram negative aerobic bacteria. (Ofloxacin tablets are not the drug of first choice in pneumonia caused by *Streptococcus pneumoniae*, *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*);
• Upper and lower urinary tract infections, including uncomplicated (cystitis) and complicated urinary tract infections.
• Uncomplicated urethral and cervical gonorrhoea, non-gonococcal urethritis and cervicitis.
Consideration should be given to official guidance on the appropriate use of anti-bacterial agents.

Ornidazole
- Bacterial vaginosis (non-specific vaginitis).

- Trichomoniasis. Genitourinary infections in women and men due to *Trichomonas vaginalis*.
- 3Amoebiasis. All intestinal infections due to *Entamoeba histolytica*, including amoebic dysentery.
- All extraintestinal forms of amoebiasis, especially amoebic liver abscess.
- Giardiasis.
- Infections due to anaerobic bacteria. Treatment of infections such as septicaemia, meningitis, peritonitis, postoperative wound infections, puerperal sepsis, septic abortion, and endometritis, with demonstrated or suspected involvement of susceptible bacteria.
- Prophylaxis during surgical interventions, particularly those involving the colon, and in gynaecological operations.

4.2 Posology and method of administration

Posology

- Ofloxacin (200mg) and Ornidazole (500mg) Fixed Dose Combination

One tablet of Ofloxacin and ornidazole combination is recommended as twice daily therapy.

Method of administration: Oral Route

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

- Ofloxacin

The dose of ofloxacin is determined by the type and severity of the infection. The dosage range for adults is 200 mg to 800 mg daily.

Up to 400 mg may be given as a single dose, preferably in the morning. Generally, individual doses should be given at approximately equal intervals.

In individual cases it may be necessary to increase the dose to a maximum total dose of 800 mg daily, which should be given as 400 mg twice daily, at approximately equal intervals. This may be

appropriate in infections due to pathogens known to have reduced or variable susceptibility to ofloxacin, in severe and/or complicated infections (e.g. of the respiratory or urinary tracts) or if the patient does not respond adequately.

The following doses are recommended:

Indications	*Single and Daily Doses*
Gonococcal urethritis and cervicitis due to susceptible *Neisseria gonorrhoeae*	400 mg
Uncomplicated cystitis	200 mg-400 mg daily
Acute pyelonephritis and complicated urinary tract infections	400 mg daily, increasing if necessary, to 400 mg twice a day
Community-acquired pneumonia. Acute exacerbations of chronic obstructive pulmonary disease including bronchitis.	400 mg daily, increasing, if necessary, to 400 mg twice a day
Non-gonococcal urethritis and cervicitis	400 mg daily

A single dose of 400 mg of ofloxacin is sufficient for the treatment of gonococcal urethritis and cervicitis due to susceptible *Neisseria gonorrhoeae*.

Special patient populations

Impaired renal function

Following a normal initial dose, dosage should be reduced in patients with impairment of renal function as determined by creatinine clearance or plasma creatinine level.

Creatinine Clearance	*Plasma Creatinine*	*Maintenance Dose**
20 to 50 ml/min	1.5 to 5 mg/dl	100 mg - 200 mg ofloxacin per day
<20ml/min**	>5 mg/dl	100 mg ofloxacin per day

* According to indication or dose interval

**The serum concentration of ofloxacin should be monitored in patients with severe renal impairment and dialysis patients.

Patients undergoing haemodialysis or peritoneal dialysis should be given 100 mg ofloxacin per day.

When creatinine clearance cannot be measured, it can be estimated with reference to the serum creatinine level using the Cockcroft's formula for adults

Impaired liver function

The excretion of ofloxacin may be reduced in patients with severe hepatic dysfunction (e.g. cirrhosis of the liver with ascitesIn such cases, it is recommended that the dose should not exceed 400 mg ofloxacin daily, because of possible reduction of excretion.

Elderly

No adjustment of dosage is required in the elderly other than that imposed by consideration of renal or hepatic function see section 4.4 QT interval prolongation).

Paediatric population

Ofloxacin is contraindicated for use in children or growing adolescents.

Duration

Treatment should not exceed 2 months duration.

A daily dose of up to 400 mg ofloxacin may be given as a single dose. In this case, it is preferable to administer ofloxacin in the morning.

Daily doses of more than 400 mg must be divided into two separate doses and be given at approximately equal intervals.

Method of administration

For oral use.

Ofloxacin tablets should be swallowed whole with sufficient liquid before or during meal times. They should not be taken within two hours of mineral antacids, sucralfate or metal ion preparations (aluminium, iron, magnesium or zinc), didanosine chewable or buffered tablets (for HIV), since reduction of absorption of ofloxacin can occur.

- Ornidazole

Trichomoniasis (Adults)

There are two possible therapeutic regimens:

- Single-dose therapy (for acute trichomoniasis)
- Five-day therapy (for chronic forms of trichomoniasis)

Type of Treatment	Daily Dosage
Single-Dose Therapy	3 tablets in the evening
Five- Day Therapy	2 tablets (one in the morning, one in the evening)

In all cases, the sexual partner should also be treated using the same oral dosage so as to avoid reinfection.

Children

The dosage for children is 25 mg per kg bodyweight per day, given in a single dose.

Amoebiasis

- Three-day treatment of patients with amoebic dysentery
- Five-to-ten-day treatment for all forms of amoebiasis.

Duration of Treatment	Daily Dosage	Daily Dosage
	Adults and Children over 35kg	Children up to 35kg
a) Three days	3 tablets in one evening dose Over 60 kg bodyweight: 4 tablets (2 tablets mornings and evenings)	125 mg per 3 kg body weight in one dose (equivalent to 40 mg per kg)
b) Five to ten days	2 tablets (1 tablet mornings and evenings)	125 mg per 5 kg body weight in one dose (equivalent to 25 mg per kg)

Giardiasis

Adults and children over 35 kg	**Children up to 35 kg**	
Duration of treatment: One to two days	3 tablets in the evening in one dose. (Body weight- above 35kg)	125 mg per 3 kg body weight in one dose (equivalent to 40 mg per kg) (body weight- up to 35 kg)

Anaerobic Infections

Prophylaxis: 1500 mg orally, 12 hours before surgery then 500 mg 12-hourly for 3 to 5 days postoperatively.

Method of administration

For oral use. Ofloxacin tablets should be swallowed whole with sufficient liquid before or during meal times.

4.3 Contraindications

Ornidazole

Ornidazole is contraindicated in patients with known hypersensitivity to the medicine or to other nitroimidazole derivatives.

Ofloxacin

The use of ofloxacin is contraindicated as follows:

- Hypersensitivity to the active substance, to any other fluoroquinolone antibacterials, or to any of the excipients.
- In patients with a history of epilepsy or an existing central nervous system disorder with a lowered seizure threshold.
- In patients with a history of tendon disorders related to fluoroquinolone administration
- In children or growing adolescents, and in pregnant or breastfeeding women, since animal experiments do not entirely exclude the risk of damage to the growth-plate cartilage in the growing organism cannot be entirely excluded.
- In patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity because they may be prone to haemolytic reactions when treated with quinolone antibacterial agents.

4.4 Special warnings and precautions for use

-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.

-Clostridium difficile-associated disease

Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with ofloxacin, may be symptomatic of pseudo-membranous colitis. 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 with diseases of the CNS
In case of convulsive seizures, treatment with FDC of Ofloxacin and Ornidazole combination should be discontinued.

- Caution should be exercised in patients with multiple sclerosis.

-Cardiac Disorders
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 antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
• uncorrected electrolyte imbalance (e.g. hypokalaemia, hypromagnesaemia) elderly
• cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
-Patients being treated with FDC of Ofloxacin and Ornidazole combination should not expose themselves unnecessarily to strong sunlight and should avoid UV rays (sun lamps, solaria).

-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 behavior including suicide attempt, sometimes after a single dose. In the event that a patient develops these reactions, FDC of Ofloxacin and Ornidazole combination should be discontinued and appropriate measures instituted. FDC of Ofloxacin and Ornidazole combination should be used with caution in patients with a history of psychotic disorder or in patients with psychiatric disease.

-Patients with impaired liver function
FDC of Ofloxacin + Ornidazole 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
FDC of Ofloxacin + Ornidazole should be used with caution in patients with a history of myasthenia gravis. Administration of antibiotics, especially of prolonged, may lead to proliferation of resistant microorganisms. The patient's condition must therefore be checked at regular intervals. If a secondary infection occurs, appropriate measures must be taken.

-Peripheral neuropathy
Sensory or sensorimotor peripheral neuropathy has been reported in patients receiving fluoroquinolones, including ofloxacin. FDC of Ofloxacin + Ornidazole should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.

-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.

-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. FDC of Ofloxacin and Ornidazole combination should therefore be administered with caution in such patients.

-Patients with rare hereditary disorders
Patients with rare hereditary disorders of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Ofloxacin

Antacids, Sucralfate, Metal Cations
Co-administered magnesium/aluminum antacids, sucralfate zinc or iron preparations and didanosine chewable/buffered tablets can reduce absorption of ofloxacin. Therefore, ofloxacin should be taken 2 hours before such preparations.

Theophylline, fenbufen or similar non-steroidal anti-inflammatory 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 anti-inflammatory drugs, or

other agents, which lower the seizure threshold. In case of convulsive seizures, treatment with ofloxacin should be discontinued.

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 co-administered with drugs that affect the tubular renal secretion such as probenecid, cimetidine, furosemide and methotrexate.

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, and antipsychotics) (see section 4.4 QT interval prolongation).

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, therefore, be monitored in patients treated with vitamin K antagonists because of a possible increase in the effect of coumarin derivatives (see section 4.4).

Glibenclamide
Ofloxacin may cause a slight increase in plasma glibenclamide levels when administered concurrently, it is therefore recommended that patients treated concomitantly with ofloxacin and glibenclamide be monitored particularly closely. Since hypoglycaemia is then more likely to occur, close monitoring of blood sugar levels is recommended in such cases.

Ornidazole
-Alcohol must not be ingested when taking ornidazole or for at least 3 days after discontinuing the medicine.

- Ornidazole potentiates the effect of coumarin type oral anticoagulants. The dosage of the anticoagulant has to be adjusted accordingly.

- Caution must be exercised when taking Ornidazole together with lithium, cimetidine and antiepileptic medicines such as phenytoin and phenobarbital.

-Ornidazole prolongs the muscle relaxant effect of vecuronium bromide.

4.6 Pregnancy and Lactation

Ofloxacin
Pregnancy

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 must not be used during pregnancy.

Breast-feeding
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
Pregnancy
Should not be used in pregnancy.

Nursing Mothers
No adequate trials are available to suggest the administration of either drug during breast feeding.

4.7 Effects on ability to drive and use machines

Ofloxacin
Since there have been occasional reports of drowsiness/somnolence, impairment of skills, dizziness/vertigo and visual disturbances, which 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), 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

The information given below is based on data from clinical studies and on extensive post marketing experience.

System organ class	**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	Overgrowth of non-susceptible microorganisms incl. Fungi			
Blood and lymphatic system disorders			Anaemia, Haemolytic anaemia, Leucopenia, Eosinophilia, Thrombocytopenia	Agranulocytosis, Bone marrow failure, Pancytopenia
Immune system disorders		Anaphylactic reaction**, Anaphylactoid reaction**, Angioedema**	Anaphylactic shock**, Anaphylactoid shock**	
Metabolism and Nutrition disorders		Anorexia, Hypoglycaemic coma		Hypoglycaemia in diabetics treated with hypoglycaemic agents (see section 4.4), Hyperglycaemia,
Psychiatric disorders*	Agitation, Sleep disorder, Insomnia	Psychotic disorder (e.g. hallucination), Anxiety, Confusional state, Nightmares, Depression, Delirium		Psychotic disorder and depression with self-endangering behaviour including suicidal ideation or suicide attempt (see Section 4.4), Nervousness
Nervous system disorders*	Dizziness, Headache	Somnolence, Paraesthesia, Dysgeusia, Parosmia, Memory impairment	Peripheral sensory neuropathy**, Peripheral sensory motor neuropathy**, Convulsion**, Extra-pyramidal symptoms or other	Tremor, Dykinesia, Ageusia, Syncope, Benign intracranial hypertension

			disorders of muscular coordination	(Pseudotumor cerebri)
Eye disorders*	Eye irritation	Visual disturbance		Uveitis
Ear and labyrinth disorders*	Vertigo		Tinnitus, Hearing loss	Hearing impaired
Cardiac disorders		Tachycardia		Ventricular arrhythmias and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged (see section 4.4 and 4.9)
Vascular disorders***		Hypotension		
Respiratory, thoracic and mediastinal disorders	Cough, Nasopharyngitis	Dyspnoea, Bronchospasm		Allergic pneumonitis (pneumonia), Severe dyspnoea
Gastrointestinal disorders	Abdominal pain, Diarrhoea, Nausea, Vomiting	Enterocolitis, sometimes haemorrhagic	Pseudo-membranous colitis**	Dyspepsia, Flatulence, Constipation, Pancreatitis
Hepatobiliary disorders		Hepatic enzymes increased (ALT, AST, LDH, gamma-GT and/or alkaline phosphatase), Blood bilirubin increased	Jaundice cholestatic	Hepatitis, which may be severe, ** Severe liver injury, including cases of acute liver failure, sometimes fatal, have been reported with ofloxacin, primarily in patients with underlying liver disorders (see section 4.4).

Skin and subcutaneous tissue disorders	Pruritus, Rash	Urticaria, Hot flushes, Hyperhidrosis, Pustular rash	Erythema multiforme, Toxic epidermal necrolysis, Photo-sensitivity reaction*, Drug eruption, Vascular purpura, Vasculitis, which can lead in exceptional cases to skin necrosis (vasculitis presents generally with petechiae, bleeding vesicles and small pimples with scabs and may even affect internal organs).	Stevens-Johnson syndrome, Acute generalised exanthemous pustulosis, Drug rash, Stomatitis, Exfoliative dermatitis
Musculoskeletal and connective tissue disorders*		Tendonitis	Arthralgia, Myalgia, Tendon rupture (e.g. Achilles tendon) as is the case with fluoroquinolones, this effect 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, familial and genetic disorders				Attacks of porphyria in patients with porphyria
General disorders and administration site conditions*				Asthenia, Pyrexia, Pain (including pain in back, chest and extremities)

Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendinitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia and neuralgia, fatigue, psychiatric symptoms (including sleep disorders, anxiety, panic attacks, depression and suicidal ideation), memory and concentration impairment, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors.

Ornidazole

Key: Very common (≥1/10), 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 the available data)

Diseases of the vascular and lymph system

Rare: Leukopenia

Nervous system disorders

Very rare: Somnolence, headache, dizziness, tremor, rigidity, coordination impairments, seizures, fatigue, vertigo, temporary loss of consciousness and sensory or mixed peripheral neuropathy.

Gastrointestinal disorders

Uncommon: Nausea, vomiting, diarrhoea, epigastric discomfort, dry mouth, loss of appetite.

Rare: Impairment of the sense of taste

Hepatobiliary diseases

Unknown: Jaundice, abnormal liver function tests

Skin and subcutaneous tissue diseases

Rare: Pruritus and skin reactions

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of benefit/risk balance of the medicinal product. Health care professionals are asked to report any suspected adverse reactions via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Ofloxacin

Symptoms

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

CNS effects including confusional state, convulsion, hallucination, and tremor have been observed in post marketing experience.

Management

In the case of overdose steps to remove any unabsorbed ofloxacin e.g. gastric lavage, administration of adsorbants and sodium sulphate, if possible during the first 30 minutes, are recommended; antacids are recommended for protection of the gastric mucosa.
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. A fraction of ofloxacin may be removed from the body with haemodialysis. Peritoneal dialysis and CAPD are not effective in removing ofloxacin from the body. No specific antidote exists.

Elimination of ofloxacin may be increased by forced diuresis.

Ornidazole

In the event of overdose, the symptoms referred to under section 4.8 Undesirable Effects occur with greater severity.
There is no specific antidote to ornidazole. In the event of cramps occurring, it is recommended that diazepam be given.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Ofloxacin

Pharmacotherapeutic group: Quinolone Antibacterial Fluoroquinolones
ATC code: J01MA01

Mechanism of action

It is a broad-spectrum anti-infective agent that belongs to the fluoroquinolones group. Ofloxacin acts on both Gram-positive and Gram-negative bacteria. Ofloxacin inhibits bacterial DNA replication by inhibiting bacterial topoisomerases, particularly DNA gyrase and topoisomerase IV. It is active after oral administration.
Therapeutic doses of ofloxacin are devoid of pharmacological effects on the voluntary or autonomic nervous system.

Resistance

Resistance to ofloxacin is acquired in a multi-step process at the target site through mutations in the two type II topoisomerases, DNA gyrase

and topoisomerase IV. Other mechanisms of resistance such as permeability barriers (common in Pseudomonas aeruginosa) and efflux systems may also influence susceptibility to ofloxacin.
The prevalence of resistance may vary based on geographical and temporal data for a given species. It is recommended that information about local resistance be obtained, in particular for the treatment of serious infections. If necessary, the opinion of an expert can be requested when the local prevalence of resistance is such that the usefulness of the product is uncertain, at least for certain types of infections.
Susceptibility testing breakpoints
MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for ofloxacin and are listed here.

PK-PD relationship
Fluoroquinolones have a dose-dependent bactericidal activity with a moderate post-antibiotic effect. For this class of antibiotics, the ratio between the area under the curve (AUC) and the minimum inhibitory concentration (MIC) or between the maximum concentration (Cmax) and the MIC is predictive of clinical success.

Bacteriological activity
The following pathogens may be considered susceptible:
- *Methicillin-susceptible Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *Neisseria gonorrhoeae*
- *Neisseria meningitidis*
- *Haemophilus influenzae*
- *Escherichia coli*
- *Klebsiella*
- *Enterobacter, Citrobacter*
- *Proteus (indole-negative and indole-positive)*
- *Salmonella, Shigella*
- *Yersinia enterocolitica*
-*Campylobacter jejuni*
- *Vibrio cholerae*
- *Vibrio parahaemolyticus*
- *Hafnia spp.*
- *Aeromonas spp.*
- *Plesiomonas spp.*
- *Chlamydiae*
- *Legionella pneumophila.*

Moderately susceptible bacteria include:
- *Serratia marcescens*
- *Enterococcus faecium*
- *Clostridium tetani*
- *Enterococci*
- *Streptococcus pyogenes*

- *Streptococcus pneumoniae*
- *Pseudomonas aeruginosa*
- *Acinetobacter*
- *Mycoplasma pneumoniae*
- *Streptococcus viridans*
- *Mycoplasma hominis*
- *Mycobacterium tuberculosis*
- *Mycobacterium fortuitum.*

Bacteria that can be considered resistant:

- *Fusobacterium spp.*
- *Eubacterium spp.*
- *Peptococci*
- *Peptostreptococci*
- *Treponema pallidum*
- *Clostridium difficile*
- *Nocardia asteroids*
- *Bacteroides spp.*
- *Ureaplasma urealyticum.*

In the case of urinary tract infection, an MIC < 16 μg/mL can still be considered susceptible.

Ornidazole

Pharmacotherapeutic group: Antiprotozoals, Nitroimidazole derivatives; ATC code: P01AB03

Mechanism of action

Ornidazole is an antiprotozoal and antibacterial agent; it is a derivative of 5- nitroimidazole. It is effective against *Trichomonas vaginalis*, Entamoeba histolitica, *Giardia lamblia* (Giardia intestinalis) and some other anaerobic bacteria, such as *Gardnerella vaginalis*, *Bacteroides* and *Clostridium spp., Fusobacterium spp.*, and anaerobic coccus. By mechanism of action ornidazole is a DNA-tropic agent with selective activity against microorganisms, which have enzyme systems able to renew nitro group and catalyze an interaction of ferredoxin proteins with nitrocompounds. After preparation penetration into microbial cell the mechanism of its action is cause by renovation of nitro group under an influence of nitroreductase of microorganism and activity of renewed nitroimidazole. Products of renovation form complexes with DNA, causing its degradation, disturb processes of replication and transcription of DNA. In addition, products of preparation metabolism have cytostatic properties and disturb processes of cell respiration.

5.2 Pharmacokinetic properties

Ofloxacin

Absorption

The administration of oral doses to fasting volunteers was followed by a rapid and almost complete absorption of ofloxacin. The peak plasma

concentration after a single oral dose of 200 mg averaged 2.6 µg/ml and was reached within one hour. The plasma elimination half-life was 5.7 to 7 hours and was not dose related.

Distribution
The apparent distribution volume was 120 litres. The plasma concentration did not materially rise with repeat doses (accumulation factor for twice daily dosage: 1.5). The plasma protein binding was approx. 25%.

Biotransformation
The biotransformation of ofloxacin was below 5%. The two main metabolites found in the urine were N-desmethyl-ofloxacin and ofloxacin-N-oxide.

Elimination

Excretion is primarily renal.

Between 80 and 90% of the dose were recovered from the urine as unchanged substance.

Ofloxacin was present in the bile in glucuronidised form. The pharmacokinetics of ofloxacin after intravenous infusion are very similar to those after oral doses. The plasma half-life is prolonged in persons with renal insufficiency; total and renal clearance decrease in accordance with the creatinine clearance. In renal insufficiency the dose should be reduced.

No clinically relevant interactions were seen with food and no interaction was found between ofloxacin and theophylline.

Ornidazole
Absorption
Ornidazole is rapidly absorbed. Mean absorption is 90%. Peak plasma concentrations are reached within three hours.

Distribution
The mean volume of distribution after i.v. 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 1000 mg every twelve hours to healthy volunteers, an accumulation factor of 1.5-2.5 was calculated.

Metabolism
Ornidazole is mainly metabolised to 2-hydroxymethyl and a-hydroxymethyl metabolites in the liver. Both main metabolites are less

active against Trichomonas vaginalis and anaerobic bacteria than the unchanged ornidazole.

Elimination
The half-life is about thirteen hours. 85% of a single dose is eliminated within the first five days, most of this being metabolised. 4% of the dose is excreted as unaltered substance in the urine.

5.3 Preclinical safety data

Ofloxacin
Preclinical effects in conventional studies of safety pharmacology, acute toxicity, repeated dose toxicity, reproductive studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Joint toxicity was observed at exposure in the human therapeutic range in juvenile rats and dogs. Ofloxacin exhibits a neurotoxic potential and causes reversible testicular alterations at high doses.

Mutagenicity studies showed no evidence for mutagenicity of ofloxacin. However, like some other quinolones Ofloxacin is phototoxic in animals at exposure in the human therapeutic range. The phototoxic, photomutagenic and photocarcinogenic potential of ofloxacin is comparable with that of other gyrase inhibitors.

Preclinical data from conventional genotoxicity studies reveal no special hazard to humans, carcinogen potential has not been investigated.

Reproduction toxicity
Ofloxacin has no effect on fertility, peri- or postnatal development, and therapeutic doses did not lead to any teratogenic or other embryotoxic effects in animals. Ofloxacin crosses the placenta and levels reached in the amniotic fluid are about 30% of the maximal concentrations measured in maternal serum.

Ornidazole
The acute oral LD50 of ornidazole in rats is 1.780 mg/kg. Reported LD50 value for mice is 1.420 mg/kg orally. Ornidazole administrated orally in mice at a dose level of 400 mg/kg/day for 13 weeks did not produce any toxicity except weight loss. Nitro-imidazoles are generally considered mutagenic chemicals.
The nitrogen group present in nitroimidazole derivatives is considered responsible for the mutagenicity of these compounds. In a study, mutagenicity was observed with Klebsiella pneumoniae and *Salmonella typhimurium*. Ornidazole was revealed to be mutagenic in *Salmonella typhimurium*, but negative results have been observed in other tests, such as micro nucleus in mice and chromosome aberrations. Long-term carcinogenicity studies were also conducted with ornidazole (high) dose 400 mg/kg/day) by administering in rats for two years. At the end of this study no carcinogenicity was recorded for ornidazole.

Like other nitroimidazoles, ornidazole is widely distributed in the body, cross the placenta and appears in breast milk. When administered during pregnancy, no teratogenic effect was observed with ornidazole in mice, rats and rabbits. Ornidazole has the advantage of fewer side effects in rats in which species its antifertility action has been documented. It has contraceptive properties in male, but not female, rats. It produces infertility by inhibiting epididymal sperm motility in terms of decreased sperm velocity. These effects are rapidly reversible after the cessation of treatment.

6. Pharmaceutical Particulars

6.1 List of Excipients

1	Maize Starch BP
2	Sodium starch Glycolate BP
3	Magnesium Stearate BP
4	Talc BP
5	Collodial Anhydrous Silica BP
6	Cross carmellose sodium BP
7	Microcrystalline Cellulose BP
8	Sheffcoat Orange 5Y600768 In-House
9	Purified Water BP

6.2 Incompatibilities

None.

6.3 Shelf-Life

24 months.

6.4 Special Precautions for storage

Store below 300C. Protect from light.

6.5 Nature and Content of container

PVC blister of 10 tablets. 1 such PVC blister are packed in a printed mono carton along with the pack insert. 10 such mono carton in a printed outer carton.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of per local requirements.

7. Marketing Authorization Holder

Company name: ALKEM LABORATORIES LTD.

Address: ALKEM HOUSE, Senapati Bapat Marg, Lower Parel, Mumbai - 400 013, India.
Telephone No.: + 91 – 22 – 3982 9999
Telefax No.: + 91 – 22 – 2495 9999
E-mail: www.alkemlabs.com

8. Marketing Authorization Number
CTD9731

9. Date of first authorization/renewal of the authorization
09/02/2024

10. Date of revision of the text
11/05/2025