For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

℞ Metronidazole and Ofloxacin Tablets

metrogyl® O

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS

Fluoroquinolones, including Ofloxacin, have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together, including:

- Tendinitis and tendon rupture
- Peripheral neuropathy
- Central nervous system effects
  Discontinue Ofloxacin immediately and avoid the use of fluoroquinolones, including Ofloxacin, in patients who experience any of these serious adverse reactions
- Fluoroquinolones, including Ofloxacin, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid Ofloxacin in patients with a known history of myasthenia gravis.
- Because fluoroquinolones, including Ofloxacin, have been associated with serious adverse reactions, reserve Ofloxacin for us e in patients who have no alternative treatment options for the following indications:
  - Acute exacerbation of chronic bronchitis
  - Uncomplicated cystitis

Fluoroquinolone may cause Low blood sugar and Mental health related side effects.

Metronidazole has been shown to be carcinogenic in mice and rats. Unnecessary use of the drug should be avoided.

COMPOSITION

Each film coated tablet contains:
Metronidazole IP ……. 500 mg
Ofloxacin IP ……..…… 200mg
Excipients …..…… q.s.
Colour: Sunset Yellow Lake

DOSAGE FORM

Film coated tablet.

INDICATIONS

For the treatment of diarrhoea of mixed infection in adult patients

DOSAGE AND METHOD OF ADMINISTRATION

One tablet twice-daily or as directed by the physician.

USE IN SPECIAL POPULATIONS

Pregnancy and Lactation

FDC of Metronidazole and Ofloxacin is contraindicated during pregnancy and lactation.

Renal impairment

FDC of Metronidazole and Ofloxacin should be used with caution in patients with renal impairment and dialysis patients.

Liver impairment

FDC of Metronidazole and Ofloxacin should be used with caution in patients with impaired liver function, as liver damage may occur.
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.

CONTRAINDICATIONS

FDC of Metronidazole and Ofloxacin is contraindicated in

- Patients with known hypersensitivity to Ofloxacin or Metronidazole or to any of the excipients of the product.
- Patients with epilepsy.
- Patients with history of tendon disorders related to fluoroquinolone administration.
- Pregnancy and breast-feeding 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.
- Patients with pre-existing CNS lesions involving a lowered convulsion threshold.
- Patients with active or chronic severe peripheral and central nervous system diseases due to the risk of neurological aggravation.
- Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity because they may be prone to hemolytic reactions when treated with quinolone antibacterial agents.

WARNINGS & PRECAUTIONS

Ofloxacin:
The use of ofloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products. Treatment of these patients with ofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.
Ofloxacin is not the drug of first choice in pneumonia caused by Streptococcus pneumoniae or Chlamydia pneumoniae.
Prolonged, disabling and potentially irreversible serious adverse drug reactions: Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. Ofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.
Tendinitis and tendon rupture: Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided. 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. At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with ofloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.
Peripheral neuropathy: Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with ofloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition.
Myasthenia gravis: Fluoroquinolones, including ofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Postmarketing 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.
CNS Effects: Fluoroquinolones, including ofloxacin, have been associated with an increased risk of CNS effects, including convulsions, increased intracranial pressure (including pseudotumour cerebri), and toxic psychoses. Quinolones may also cause CNS stimulation, which may lead to tremors, restlessness, light-headedness, confusion, and hallucinations. If these reactions occur in patients receiving ofloxacin, the drug should be discontinued and appropriate measures instituted.
The effects of ofloxacin on brain function or on the electrical activity of the brain have not been tested. Therefore, until more information becomes available, ofloxacin, like all other quinolones, should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis, epilepsy, and other factors that predispose to seizures.
The safety and efficacy of ofloxacin in paediatric patients and adolescents (under the age of 18 years), pregnant women, and lactating women has not been established.
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 of ofloxacin. 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 predisposed to seizures: Quinolones may lower the seizure threshold and may trigger seizures. Ofloxacin is contraindicated in patients with a history of epilepsy or with a known predisposition to seizures and, as with other quinolones; ofloxacin should be used with extreme caution in patients predisposed to seizures.
Patients with a known predisposition to seizures may include those with pre-existing central nervous system lesions, concomitant treatment with fenbufen and similar non-steroidal anti-inflammatory drugs (NSAIDs), or with drugs which lower the cerebral seizure threshold, such as theophylline. In case of convulsive seizures, treatment with ofloxacin should be discontinued.
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.
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:
- 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.
- Uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- 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)
- Cardiac disease (e.g. heart failure, myocardial infarction, bradycardia).

Aortic aneurysm and dissection: Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis). In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.
Superinfection: As with other antibiotics, the use of ofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms, especially Enterococci, resistant strains of some organisms or Candida. Repeated evaluation of the patient's condition is essential and periodic in vitro susceptibility tests may be useful. If secondary infection occurs during therapy, appropriate measures should be taken.
Methicillin-resistant S. aureus: Methicillin-resistant S. aureus is 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).
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.
Streptococcus pneumoniae, β-haemolytic Streptococci and Mycoplasma: 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 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.
Diseases caused by Clostridioides difficile: Diarrhoea, especially if severe, persistent and/or bloody, occurring during or after treatment with ofloxacin (including several weeks after treatment), may indicate a condition caused by Clostridioides difficile, the most severe form of which is pseudomembranous colitis (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of 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 pseudomembraneous colitis is suspected, treatment should be discontinued immediately.
Appropriate specific antibiotic therapy must be started without delay (e.g. oral vancomycin, oral teicoplanin or metronidazole). Medicinal products that inhibit peristalsis are contraindicated in such cases.
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.
Patients with impaired renal function: Since ofloxacin is eliminated primarily via the kidneys, the dose should be adjusted in patients with impaired renal function.
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, pruritus 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.
Prevention of photosensitization: Photosensitization 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.
Dysglycaemia: As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia 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.
Interference with laboratory tests: In patients treated with ofloxacin, determination of opiates or porphyrin levels in urine may give false-positive results. It may be necessary to confirm positive opiate or porphyrin screens by more specific methods.
Vision disorders: If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.
Metronidazole:
• Patients should abstain from alcohol for at least 48 hours following discontinuation of therapy with metronidazole. A disulfiram-like reaction with hypotension and flushing has occurred.
• Caution is advised in patients with porphyria.
• Metronidazole tablets should not be used in patients with blood dyscrasias or with active non-infectious disease of the central nervous system. High doses of metronidazole may mask the presence of syphilis.
• Caution in patients with epilepsy or those who have had seizures as high doses of Metronidazole can induce seizures.
• Use with caution in the second and third trimester when used to treat trichomoniais or bacterial vaginosis.
• Regular clinical and laboratory surveillance are advised if treatment continues for more than 10 days.
• Consideration of the therapeutic benefit against the risk of peripheral neuropathy is advised with continuous therapy for chronic conditions.
• There is a possibility that after *Trichomonas vaginalis* has been eliminated a gonococcal infection might persist.
• The elimination half-life of metronidazole remains unchanged in the presence of renal failure. The dosage of metronidazole, therefore, needs no reduction. Such patients, however, retain the metabolites of metronidazole. The clinical significance of this is not known at present.
• In patients undergoing haemodialysis metronidazole and metabolites are efficiently removed during an eight-hour period of dialysis. Metronidazole should, therefore, be readministered immediately after haemodialysis.
• No routine adjustment in the dosage of metronidazole need be made in patients with renal failure undergoing intermittent peritoneal dialysis (IPD) or continuous ambulatory peritoneal dialysis (CAPD).
• Metronidazole is mainly metabolised by hepatic oxidation. Substantial impairment of metronidazole clearance may occur in the presence of advanced hepatic insufficiency. Signficant cumulation may occur in patients with hepatic encephalopathy and the resulting high plasma concentrations of metronidazole may contribute to symptoms of the encephalopathy. Therefore, metronidazole should be administered with caution to patients with hepatic encephalopathy. The daily dosage should be reduced to one third and may be administered once daily.
• Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should therefore be used after careful benefit-risk assessment and only if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued. Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole.
• Patients should be warned that metronidazole may darken urine.
• Due to inadequate evidence on the mutagenicity risk in humans, the use of metronidazole for longer treatment than usually required should be carefully considered.

DRUG INTERACTIONS

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).
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.
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.

Metronidazole:
Combinations to be used with caution:
Lithium: Lithium retention accompanied by evidence of possible renal damage has been reported in patients treated simultaneously with lithium and metronidazole. Lithium treatment should be tapered or withdrawn before administering metronidazole. Plasma concentration of lithium, creatinine, and electrolytes should be monitored in patients under treatment with lithium while they receive metronidazole.

Anticoagulants: Some potentiation of anticoagulant therapy has been reported when metronidazole has been used with the warfarin type oral anticoagulants. Dosage of the latter may require reducing. Prothrombin times should be monitored. No interactions have been reported with anticoagulants of the heparin type. However, anticoagulant activity should be routinely monitored with these products.
Alcohol: Patients should be advised not to take alcohol during metronidazole therapy and for at least 48 hours after because of the possibility of a disulfiram-like reaction.
Disulfiram: Psychotic reactions have been reported.
Immunosuppressants: Patients receiving ciclosporin are at risk of elevated ciclosporin serum levels. Serum ciclosporin and serum creatinine should be closely monitored when coadministration is necessary.

Pharmacokinetic interactions:
Antiepileptics: Patients receiving phenobarbital metabolise metronidazole at a much greater rate than normally, reducing the half-life to approximately 3 hours. Metronidazole inhibits metabolism of phenytoin (increases plasma phenytoin concentration). Primidone accelerates the metabolism of Metronidazole causing reduced plasma concentrations.
Cytotoxics: Metronidazole inhibits metabolism of fluorouracil. Therefore, increased toxicity of fluorouracil can result.
Ulcer-healing drugs: Cimetidine inhibits the metabolism of metronidazole (increases plasma-metronidazole concentration).
Oestrogens: broad spectrum antibiotics possibly reduce the contraceptive effect.
Drug-lab modifications: Aspartate amino transferase assays may give spuriously low values in patients taking metronidazole, depending on the method used.

UNDESIRABLE EFFECTS

Ofloxacin
Low blood sugar and mental health related side effects: The drug may cause low blood sugar and mental health related side effects. Low blood sugar levels, also called as hypoglycemia, can lead to coma. The mental health side effects are more prominent and more consistent across the systemic fluoroquinolone drug class. The mental side effects to fluoroquinolones are:
Disturbance in attention,
Disorientation,
Agitation,
Nervousness,
Memory impairment,
Serious disturbances in mental abilities called delirium.
Stevens-Johnson syndrome or Toxic epidermal necrolysis: Cases of severe bullous skin reactions such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) 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.
The information given below is based on data from clinical studies and on extensive post marketing experience.
The frequency of adverse events listed below is defined using the following convention:
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).
Infections and infestations: Uncommon: Fungal infection, Pathogen resistance.
Blood and lymphatic system disorders: Very rare: Anaemia, haemolytic anaemia, leucopenia, eosinophilia, and thrombocytopenia. Not known: Agranulocytosis, bone marrow failure, pancytopenia.
Immune system disorders: Rare: Anaphylactic reaction*, anaphylactoid reaction*, angioedema*. Very rare: Anaphylactic shock*, anaphylactoid shock*.
Metabolism and Nutrition disorders: Rare: Anorexia. Not known: Hypoglycaemia in diabetics treated with hypoglycaemic agents, Hyperglycaemia, Hypoglycaemic coma.
Psychiatric disorders**: Uncommon: Agitation, sleep disorder, insomnia. Rare: Psychotic disorder (for e.g. hallucination), anxiety, confusional state, nightmares, depression. Not known: Psychotic disorder and depression with self-endangering behaviour including suicidal ideation or suicide attempt, nervousness.
Nervous system disorders**: Uncommon: Dizziness, headache. Rare: Somnolence, paraesthesia, dysgeusia, parosmia. Very rare: Peripheral sensory neuropathy*, peripheral sensory motor neuropathy*, convulsion*, extra-pyramidal symptoms or other disorders of muscular coordination. Not known: Tremor, dykinesia, ageusia, syncope, benign intracranial hypertension (pseudotumor cerebri).
Eye disorders**: Uncommon: Eye irritation. Very rare: Visual disturbance. Not known: Uveitis.
Ear and labyrinth disorders**: Uncommon: Vertigo. Very rare: Tinnitus, hearing loss. Not known: Hearing impaired.
Cardiac disorders: Rare: Tachycardia. Not known: Ventricular arrhythmias and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged.
Vascular disorders: Rare: Hypotension.
Respiratory, thoracic and mediastinal disorders: Uncommon: Cough, Nasopharyngitis. Rare: Dyspnoea, bronchospasm. Not known: Allergic pneumonitis, severe dyspnoea.
Gastrointestinal disorders: Uncommon: Abdominal pain, diarrhoea, nausea, vomiting. Rare: Enterocolitis, sometimes haemorrhagic. Very rare: Pseudomembranous colitis*. Not known: Dyspepsia, flatulence, constipation, pancreatitis.
Hepatobiliary disorders: Rare: Hepatic enzymes increased (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase), blood bilirubin increased. Very rare: Jaundice cholestatic. Not known: 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.
Skin and subcutaneous tissue disorders: Uncommon: Pruritus, rash. Rare: Urticaria, hot flushes, hyperhidrosis, pustular rash. Very rare: Erythema multiforme, toxic epidermal necrolysis, photo-sensitivity reaction*, drug eruption, vascular purpura, vasculitis, which can lead in exceptional cases to skin necrosis. Not known: Stevens-Johnson syndrome, acute generalised exanthemous pustulosis, drug rash, stomatitis, exfoliative dermatitis.
Musculoskeletal and connective tissue disorders**: Rare: Tendonitis. Very rare: Arthralgia, myalgia, tendon rupture (e.g. Achilles tendon) which may occur within 48 hours of treatment start and may be bilateral. Not known: Rhabdomyolysis and/or myopathy, muscular weakness, muscle tear, muscle rupture, ligament rupture, arthritis.
Renal and urinary disorders: Rare: Serum creatinine increased. Very rare: Acute renal failure. Not known: Acute interstitial nephritis.
Congenital, familial and genetic disorders: Not known: Attacks of porphyria in patients with porphyria.
General disorders and administration site conditions**: Not known: Asthenia, pyrexia, pain (including pain in back, chest and extremities).
* post marketing experience
** 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, depression, fatigue, memory impairment, sleep disorders, 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.
Metronidazole
The frequency of adverse events listed below is defined using the following convention:
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).

Blood and lymphatic system disorders: Very rare: Agranulocytosis, neutropenia, thrombocytopenia, pancytopenia. Not known: Leucopenia, bone marrow depression disorders such as aplastic anaemia.

Immune system class: Rare: Anaphylaxis. Not known: Angiodema, urticaria, fever.

Metabolism and nutrition disorders: Not known: Anorexia.

Psychiatric disorders: Very rare: Psychotic disorders, including confusion and hallucinations. Not known: Depressed mood.

Nervous system disorders; Very rare: Encephalopathy (eg. confusion, fever, headache, paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebellar syndrome (eg. ataxia, dysathria, gait impairment, nystagmus and tremor) which may resolve in discontinuation of the drug, drowsiness, dizziness, convulsions, headaches. Not known: Depression, paraesthesia, during intensive and-or prolonged metronidazole therapy, peripheral sensory neuropathy or transient epileptiform seizures have been reported. In most cases neuropathy disappeared after treatment was stopped or when dosage was reduced. Incoordination of movement, aseptic meningitis.

Eye disorders: Very rare: Diplopia, myopia. Not Known: Optic neuropathy/neuritis.

Ear and labyrinth disorders: Not known: Hearing impaired/hearing loss (including sensorineural), tinnitus.

Gastrointestinal disorders: Not known: Unpleasant taste in the mouth, taste disorders, oral mucositis, furred tongue, nausea, vomiting, gastro-intestinal disturbances, diarrhoea, abdominal pain, anorexia.

Hepatobiliary disorders: Very rare: Abnormal liver function tests, cholestatic hepatitis, jaundice and pancreatitis which is reversible on drug withdrawal, cases of liver failure requiring liver transplant have been reported in patients treated with metronidazole in combination with other antibiotic drugs.

Skin and subcutaneous tissue disorders: Very rare: Skin rashes, pustular eruptions, pruritus, flushing. Not known: Erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis, fixed drug eruption.

Musculoskeletal, connective tissue and bone disorders: Very rare: Myalgia, arthralgia.

Renal and urinary disorders: Very rare: Darkening of urine (due to metronidazole metabolite).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbcpl.com

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.

Metronidazole:
Features:
Nausea, vomiting, diarrhoea, anorexia, metallic taste, headache, dizziness and occasionally insomnia and drowsiness. Transiently increased liver enzyme activities have been reported rarely.
Transient epileptiform seizures have been reported following intensive or prolonged therapy. Other adverse effects occurring in these circumstances include peripheral motor neuropathy, blood dyscrasias and liver damage.
The combination of alcohol and metronidazole has been said to cause disulfiram type reactions in about 10% of individuals with sudden onset of excitement, giddiness, flushing, nausea, headache, hypotension and dyspnoea.
However, the mechanism of this reaction has been questioned.
Treatment:
Unlikely to be required.
Disulfiram type reactions should be treated with intravenous fluids and plasma expanders if necessary. Symptomatic and supportive.
In more serious cases:
1. Single brief convulsions do not require treatment. If frequent or prolonged control with intravenous diazepam (10-20mg in adults; 0.1-0.3mg/kg body weight) or lorazepam (4mg in an adult and 0.05mg/kg in a child). Give oxygen and correct acid base and metabolic disturbances as required.
2. Other measures as indicated by the patient's clinical condition

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Pharmacological class: Nitroimidazole/ Fluoroquinolone

Pharmacodynamics

Ofloxacin:
Ofloxacin is belongs to quinolone/fluoroquinolone class of antibiotics. Ofloxacin is bactericidal and its mode of action depends on blocking of bacterial DNA replication by binding itself to an enzyme called DNA gyrase, which allows the untwisting required to replicate one DNA double helix into two. Notably the drug has 100 times higher affinity for bacterial DNA gyrase than for mammalian. Ofloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. Ofloxacin acts on DNA gyrase and topoisomerase IV, enzymes which, like human topoisomerase, prevents the excessive supercoiling of DNA during replication or transcription. By inhibiting their function, the drug thereby inhibits normal cell division.

Metronidazole:
Metronidazole has antiprotozoan and antibacterial effects. It is effects against *Trichomonas vaginalis, Gardnerella vaginalis* and other protazoa including *Entamoeba histolytica, Gardia lamblia* and anaerobic bacteria.

Pharmacokinetic Properties

Ofloxacin
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. 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%. The biotransformation of ofloxacin was below 5%. The two main metabolites found in the urine were N-desmethyl-ofloxacin and ofloxacin-N-oxide. 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.
Metronidazole:
Absorption
Metronidazole is readily absorbed following administration by mouth and bioavailability is 90-100%. Peak plasma concentrations of approximately 5µg/ml and 10µg/ml are achieved an average of 1-2 hours after single doses of 250mg and 500mg respectively. Some accumulation and consequently higher concentrations occur when multiple doses are given. Absorption may be delayed, but is not reduced overall, by administration with food.
Distribution
Metronidazole is widely distributed. It appears in most body tissues and fluids. It also crosses the placenta and rapidly enters foetal circulation. No more than 20% is bound to plasma proteins.
Biotransformation
Metronidazole is metabolised in the liver by side-chain oxidation and glucuronide formation.
The plasma elimination half-life of metronidazole is about 6-9 hours; that of the hydroxy metabolite is slightly longer. The half-life of metronidazole is reported to be longer in neonates and in patients with severe liver disease.
Elimination
The majority of a dose of metronidazole is excreted in the urine, mainly as metabolites; a small amount appears in the faeces. Metronidazole can be used in chronic renal failure; it is rapidly removed from the plasma by dialysis. Metronidazole is excreted in milk but the intake of a suckling infant of a mother receiving normal dosage would be considerably less than the therapeutic dosage for infants.

INCOMPATIBILITIES

None known.

PACKAGING INFORMATION

Blister of 10 Tablets

STORAGE AND HANDLING INSTRUCTIONS

Store in a cool, dry place. Protect from light.

Manufactured in India by:
J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, 'B' Wing, Hind Cycle Road, Worli, Mumbai - 400 030, India.
® Regd. Trade Mark

Note: This prescribing information is applicable for India Market only.

Date: April 2025