For the use of a Registered Medical Practitioner only

℞ Ofloxacin and Ornidazole Tablets IP

nor-metrogyl® plus

Warning: Serious Adverse Reactions, Including Tendinitis, Tendon Rupture, Peripheral Neuropathy, Central Nervous System (CNS) Effects and Exacerbation Of Myasthenia Gravis.

See full prescribing information forcomplete boxed warning.

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; and,
- CNS effects.

Discontinue ofloxacin immediately and avoid the use of fluoroquinolones, including ofloxacin, in patients who experience any of theseserious adverse reactions.

Fluoroquinolones, including ofloxacin, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid ofloxacin in patients with a known historyofmyasthenia gravis.

Because fluoroquinolones, including ofloxacin, have been associated with serious adverse reactions, reserve ofloxacin for use in patients who have no alternative treatment options for the following indications:

- Acute exacerbation of chronic bronchitis.
- Uncomplicated cystitis.

This drug may cause low blood sugar and mental health-related side effects.

COMPOSITION

Each film coated tablet contains:

Ornidazole IP ..... 500 mg

Ofloxacin IP ..... 200 mg

Excipients ..... q.s.

Colours : Sunset Yellow FCF

PHARMACEUTICAL FORM

Film Coated Tablet.

THERAPEUTIC INDICATION

It is indicated for the treatment of diarrhea of mixed infection in adult only.

DOSAGE AND ADMINISTRATION

The recommended adult dosage is 1 tablet as twice-daily therapy or as directed by the Physician. Method of administration: For oral use only.

Patients should be instructed to swallow the tablet whole and must not be chewed or crushed.

CONTRAINDICATIONS

It is contraindicated in patients with known hypersensitivity to ofloxacin or ornidazole or any member of the quinolone or nitroimidazole group of antimicrobial agents or any other component of the formulations.

The use of ofloxacin is contraindicated in followings: In patients with a history of epilepsyor an existing central nervous system disorder with a lowered seizure threshold; and 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.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

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 tendinit is 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 fluoroquinoloneuse 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 predis position 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 Ole-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 Ill 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.

Ofloxacin is not the drug of first choice in pneumonia caused by Streptococcus pneumoniae or Chlamydia pneumoniae.

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).

Resistancetofluoroquinolones of £. co/i: 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£.coli to fluoroquinolones.

Streptococcus pneumoniae, B-haemolytic Streptococci and Mycoplasma: Ofloxacin is not the drug of first choice for pneumonia caused by Pneumococci or Mycoplasma or infection caused by -haemolytic Streptococci.

Neisseria gonorhoeae 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 pseudomembraneouscolitis 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 contra indicated in such cases.

Severe bullaus 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 renalfunction: 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, pruritusor 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 comb ination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomitantly.

Prevention of photosensitization: Photosensitizat ion 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 discontinuationin 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. Ornidazole

Ornidazole must be used with caution in patients with diseases of the CNS (e.g., epilepsy or multiple sclerosis) and liver disease. The effect of other medicines can be intensified or impaired.

DRUG INTERACTION

Ofloxacin

Antacids, Sucra/fate, 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 ta 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 Ill 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.

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.

USE IN SPECIFIC POPULATION

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.

There is no clinical data available for ornidazole exposure in pregnancy. Studies conducted on animals do not demonstrate direct or indirect harmful effects on pregnancy/embryonic/foetal development/birth or post-natal development. The effect of ornidazole on women of childbearing potential or birth control methods is unknown. Extensive studies in various species have revealed no sign of any teratogenic or foetotoxic action of ornidazole. However, no controlled studies have been carried out in pregnant women. As a matter of principle, ornidazole should not be prescribed in early pregnancy or to nursing mothers except when absolutely necessary.

Lactation

Ofloxacin is excreted into human breast milk in small amounts. Because of the potential for arthropathy and other serious toxicity in the nursinginfant, breast-feedingshould be discontinued during treatment with ofloxacin.

It is not known whether ornidazole is excreted in human milk. The excretion of ornidazole via milk in animals has not been researched. In making the decision whether or not to discontinue breastfeeding or whether or not ornidazole treatment should be discontinued/avoided, the benefit of breastfeeding to the infant and the benefit of ornidazole treatment for the nursing mother must be considered.

Paediatric Use

Safety and effectiveness in paediatric patients and adolescents below the age of 18 years have not been established. Ofloxacin causes arthropathy (arthrosis) and osteochondrosis in juvenile animals of several species. Ofloxacin is contraindicated for use in children or growing adolescents.

The pharmacokinetics or ornidazole in neonates and young children is similar to those in adults.

Eld erly Use

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

Geriatric patients are at increased risk for developing severe tendon disorders, including tendon rupture, when being treated with a fluoroquinolone such as ofloxacin. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles tendon, hand, shoulder or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution shou ld be used when prescribing ofloxacin to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue ofloxacin and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur.

EFFECTSON ABILITY TO DRIVE AND USE MACHINES

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.

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.

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 necro/ysis: 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 mucosaI reactions occur.

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

Infections ond infestations: Uncommon: Fungal infection , Pathogen resistance.

Blood and lymphatic system disorders: Very rare: Anaemia, haemolytic anaemia, leucopenia, eosinophilia, thrombocytopenia. Not known: Agranulocytosis, bone marrow failure, pancytopenia.

Immune system disorders: Rare: Anaphy lactic 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, Hypoglycaemiccoma.

*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 mediostino/ 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: Pseudomembranouscolitis*. Not known: Dyspepsia, flatulence, constipation, pancreatitis.

Hepotobiliory disorders: Rare: Hepatic enzymes increased (ALAT, ASAT, LOH, 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.

Reno/ and urinary disorders: Rare: Serum creatinine increased. Very rare: Acute renal failure. Not known: Acute interstitial nephritis.

Congenitol, fomiliol 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).

* postmarketing experience

** Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes mult iple, 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 theuse of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors.

Ornidazole

Adverse effects have been categorized as follows: very common (1/10), common (1/100 to <l/10), uncommon (1/1,000 to <1/100), rare (1/10,000to <1/1000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

Diseases of the Vascular and Lymph System: Rare: leucopenia.

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.

Skin and subcutaneous tissue diseases: Rare: pruritus and skin reactions. Hepotabiliory Diseases: Unknown: jaundice, abnormal liver function tests. 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@jbpharma.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, taking appropriate measures 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 CAPO are not effective in removing ofloxacin from the body. No specific antidote exists. Elimination of ofloxacin may be increased by forced diuresis.

Ornidazole

In cases of overdosage, the symptoms mentioned under Undesirable Effects occur in a more severe form. No speci fic ant idote is known. The administration of diazepam is recommended if cramps occur.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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.

Ornidazole

Ornidazole is a S-nitroimid azole derivative active against protozoa and anaerobic bacteria. It is converted to reduction products that interact with DNA to cause destruction of the helical DNA structure and strand, leading to a protein synthesis inhibition and cell death in susceptible organisms. Ornidazole is effective against *Trichomonas vagina/is, Entamoeba histolytica and Giardia /amblia (Giardia intestinalis), and also against certain anaerobic bacteria such as Bacteroides and C/ ostridium spp., Fusobacterium spp., and anaerobiccocci.*

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: LS). 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.

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 (6-36 mg/I). After repeated administration of SOO mg or 1,000 mg every 12 hours to healthy volunteers, an accumulation factor of 1.5-2.5 was calculated. Ornidazole is mainly metabolised to 2-hydroxymethyl and a-hydroxymethyl metabolites in the liver. Both main metabolites are less active against Trichomonas vagina/is and anaerobic bacteria than the unchanged ornidazole. The half-life isabout 13 hours. While 85%of a single dose is eliminated within the first 5 days (most of this being metabolised), 4% of the dose is excreted as unaltered substance in the urine.

INCOMPATIBILITIES

Not applicable.

STORAGE IN STRUCTIONS

Protect from light & moisture.

Keep out of reach of children.

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J. B. CHEMICALS & PHARMACEUTICALS LTD.
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Note: This prescribing information is applicable for India Market only

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