1. NAME OF THE MEDICINAL PRODUCT
AVROFLOX-TN CAPLET

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated caplet contains:
Ofloxacin……..200mg
Tinidazole……600mg
For a full list of excipients see section 6.1

3. PHARMACEUTICAL FORM
Oral Caplet.

Oblong, nearly white to off-white caplets marked with "AVRO AFXTN" on one side and scored on the reverse side

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Avroflox-TN is indicated for the treatment of a wide variety of infections caused by susceptible Gram-positive and Gram-negative organisms along with anaerobes and protozoa (see sections 4.4 and 5.1).
These include infections of:

- Respiratory tract infections
- Ear, nose and throat infections.
- Urinary tract infections including nongonococcal gonorrhoea and kidney infections
- Gynaecological and Genital infections including gonorrhoea, Chlamydia and chlamydophilia infections.
- Pelvic inflammatory Disease
- Post-surgical care
- Skin and soft tissue infections
- Gastrointestinal infections including diarrhoea and amoebic dysentery.
- Bone and joint infections
- Anthrax infections
- Mycobacterial infections such as leprosy
- Acute sinusitis
- Uncomplicated cervical and urethral gonorrhoea
- Thyphoid fever
- Complicated intra-abdominal infections caused by E. Coli, Pseudomonas aeruginosa, P.mirabilis, K. Pneumoniae and Bacteroides fraginalis.
- Protozoal infections such as amoebiasis, giardiasis and trichomoniasis.

Special attention should be paid to available information on resistance to Ofloxacin + Tinidazole before commencing therapy.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Posology
Route: Oral administration during or after a meal.

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to Ofloxacin/Tinidazole of the causative organism(s), the renal function of the patient and, in children and adolescents the body weight.
The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.

Treatment of infections due to certain bacteria (e.g. *Psuedomonas aeruginosa, Acinetobacter* or *Staphylococci*) may require higher doses and co-administration with other appropriate antibacterial agents.

Adults
The following doses are recommended:

Indications	*Single and Daily Doses*
Uncomplicated urethral/ cervical gonorrhoea	400mg/1200mg (2 caplets) single dose
Uncomplicated lower urinary tract infections	200mg/600mg – 400/1200mg daily
Complicated infections of the upper urinary tract	400/1200mg daily, increasing if necessary, to 400/1200mg twice a day
Lower respiratory tract infections	400/1200mg daily, increasing, if necessary, to 400/1200mg twice a day
Non-gonococcal urethritis and cervicitis	400/1200mg daily

A single dose of 400/1200mg of Ofloxacin/Tinidazole is sufficient for the treatment of uncomplicated gonorrhoea.

Paediatric population
Avroflox-TN is not recommended for those below the age of 18 years.

Elderly patients
Elderly patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.

Patients with renal and hepatic impairment
Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance	*Plasma Creatinine*	*Maintenance Dose**
20 to 50 ml/min*	1.5 to 5 mg/dl	100 -200mg/300-600mg per day
<20ml/min**	>5 mg/dl	100mg/300mg 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 100mg Ofloxacin per day.

Method of administration
Caplet should be swallowed whole and unchewed with adequate fluid. Caplets be taken during or after a meal. Patients should be advised to drink plenty of fluid. The caplets should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit-juice (e.g. calcium-fortified orange juice) (see section 4.5).

In severe cases or if the patient is unable to take caplets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous Ofloxacin/Tinidazole until a switch to oral administration is possible.

4.3 Contraindications

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.

Tinidazole
- Hypersensitivity to the active substance or to any of the excipients
- As with other drugs of similar structure, Tinidazole is contraindicated in patients having, or with a history of, blood dyscrasia, although no persistent haematological abnormalities have been noted in clinical or animal studies.
- Tinidazole should be avoided in patients with organic neurological disorders.
- Tinidazole, other 5-nitroimidazole derivatives or any of the components of this product should not be administered to patients with known hypersensitivity to the drug.
- Use of Tinidazole is contraindicated during the first trimester of pregnancy and in nursing mothers.

4.4 Special warnings and precautions for use
Ofloxacin

General
Ofloxacin tablets are not the drug of first choice in pneumonia caused by *Streptococcus pneumoniae* or *Chlamydia pneumoniae*.

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

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.

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.

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

Hypersensitivity
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.

Diseases caused by Clostridium 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 *Clostridium 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 pseudo-membraneous 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.

Patients predisposed to seizures
Quinolones may lower the seizure threshold and may trigger seizures. Ofloxacin is contraindicated in patients with a history epilepsy or with a known predisposition 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.

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 history of psychotic disorder
Psychotic reactions have been reported in patients receiving fluoroquinolones including Ofloxacin. 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 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.

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.

Superinfection
As with other antibiotics, the use of Ofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms, 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.
Prevention of photosensitisation
Photosensitisation has been reported with Ofloxacin. It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), during treatment and for 48 hours following treatment discontinuation in order to prevent photosensitisation.

QT interval prolongation
Very rare cases of QT interval proplongation 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. hypokalemia, hypomagnesemia) - 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)

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.

Peripheral neuropathy
Sensory or sensorimotor peripheral neuropathy has been reported in patients receiving fluoroquinolones, including Ofloxacin, which can be rapid in its onset. Ofloxacin should be discontinued if the patient experiences symptoms of neuropathy. This would minimise the possible risk of developing an irreversible condition.

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.

Tinidazole
As with related compounds, alcoholic beverages should be avoided during Tinidazole therapy because of the possibility of a disulfiram-like reaction (flushing, abdominal cramps, vomiting, tachycardia). Alcohol should be avoided until 72 hours after discontinuing Tinidazole.

Drugs of similar chemical structure have also produced various neurological disturbances such as dizziness, vertigo, incoordination and ataxia. If during therapy with Tinidazole abnormal neurological signs develop, therapy should be discontinued.

Carcinogenicity has been seen in mice and rats treated chronically with metronidazole, another nitroimidazole agent. Although carcinogenicity data is not available for Tinidazole, the two drugs are structurally related and therefore there is a potential for similar biologic effects. Mutagenicity results with Tinidazole were mixed (positive and negative).The use of Tinidazole for longer treatment than usually required should be carefully considered.

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 tablets. 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.

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

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.

Tinidazole

Alcohol: Concurrent use of Tinidazole and alcohol may produce a disulfiram-like reaction and should be avoided.

Anticoagulants: Drugs of similar chemical structure have been shown to potentiate the effects of oral anticoagulants. Prothrombin time should be closely monitored and adjustments to the dose of the anticoagulants should be made as necessary.

Cholestyramine may decrease oral bioavailability; separate dosing of cholestyramine and Tinidazole is recommended.

Ethyl alcohol*,* ethanol*-containing preparations,* propylene glycol*:* It is recommended that these substances not be used concurrently with Tinidazole, or for 3 days following Tinidazole therapy; abdominal cramps, nausea, vomiting, headache, or flushing may occur.

Intravenous phenytoin *or intravenous* fosphenytoin*:* Concomitant administration with Tinidazole increases half-life and decreases clearance of phenytoin.

Oxytetracycline may antagonize the therapeutic effect of Tinidazole.

Lithium concentrations may increase when Tinidazole therapy is introduced; serum lithium and serum creatinine levels should be monitored several days after beginning Tinidazole in order to detect possible lithium intoxication.

Fluorouracil*:* Tinidazole may decrease the clearance of fluorouracil (resulting in increased side effects; if co-administration cannot be avoided monitor for fluorouracil-associated toxicity.

Disulfiram*in:* It is recommended that Tinidazole not be used concurrently with, or for 2 weeks following disulfiramin in alcoholic patients; such use may result in confusion and psychotic reactions because of combined toxicity.

Cytochrome p450 inhibitors such as cimetidine or ketoconazole taken concurrently with Tinidazole may prolong half-life and decrease plasma clearance of Tinidazole

Cytochrome p450 inducers such as: Fosphenytoin, Phenobarbital, Phenytoin and rifampin taken concurrently with Tinidazole may increase elimination and decrease plasma concentration of Tinidazole.

Cyclosporine*,* tacrolimus*:* Tinidazole may increase levels of these drugs; monitor for signs of calcineurin-inhibitor associated toxicities.

4.6 Fertility, pregnancy and lactation

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.

Fertility studies in rats receiving 100mg and 300mg Tinidazole/kg had no effect on fertility, adult and pup weights, gestation, viability or lactation. There was a slight, not significant, increase in resorption rate at the 300mg/kg dose.

Tinidazole crosses the placental barrier. Since the effects of compounds of this class on foetal development are unknown, the use of Tinidazole during the first trimester is contraindicated. There is no evidence that Tinidazole is harmful during the latter stages of pregnancy, but its use during the second and third trimesters requires that the potential benefits be weighed against possible hazards to mother or foetus.

Lactating women
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.

Tinidazole is excreted in breast milk. Tinidazole may continue to appear in breast milk for more than 72 hours after administration. Women should not nurse until at least 3 days after having discontinued taking Tinidazole.

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.

Tinidazole
No special precautions should be necessary. However, drugs of similar chemical structure, including Tinidazole, have been associated with various neurological disturbances such as dizziness, vertigo, ataxia, peripheral neuropathy (paraesthesia, sensory disturbances, hypoaesthesia) and rarely convulsions. If any abnormal neurological signs develop during Tinidazole therapy, the drug should be discontinued.

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	Fungal infection, Pathogen resistance			
Blood and lymphatic system disorders			Anaemia, Haemolytic anaemia, Leucopenia, Eosinophilia, Thrombocytopenia	Agranulocytosis, Bone marrow failure, Pancytopenia
Immune system disorders		Anaphylactic reaction*, Anaphylactoid reaction*,	Anaphyl actic shock*,	

		Angioedema*	Anaphylactoid shock*	
Metabolism and Nutrition disorders		Anorexia		Hypoglycaemia in diabetics treated with hypoglycaemic agents. Hyperglycaemia, Hypoglycaemic coma
Psychiatric disorders	Agitation, Sleep disorder, Insomnia	Psychotic disorder (for e.g. hallucination), Anxiety, Confusional state, Nightmares, Depression		Psychotic disorder and depression with self-endangering behaviour including suicidal ideation or suicide attempt, Nervousness
Nervous system disorders	Dizziness, Headache	Somnolence, Paraesthesia, Dysgeusia, Parosmia	Peripheral sensory neuropathy*, Peripheral sensory motor neuropathy* , Convulsion*, Extra-pyramidal symptoms or other disorders of muscular coordination	Tremor, Dykinesia, Ageusia, Syncope
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

Vascular disorders		Hypotension		
Respiratory, thoracic and mediastinal disorders	Cough, Nasopharyngitis	Dyspnoea, Bronchospasm		Allergic pneumonitis, Severe dyspnoea
Gastrointestinal disorders	Abdominal pain, Diarrhoea, Nausea, Vomiting	Enterocolitis, sometimes haemorrhagic	Pseudomembranous colitis*	Dyspepsia, Flatulence, Constipation, Pancreatitis
Hepatobiliary disorders		Hepatic enzymes increased (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase), Blood bilirubin increased	Jaundice cholestatic	Hepatitis, which may be severe* Severe liver injury, including cases with acute liver failure, sometimes fatal, have been reported with ofloxacin, primarily in patients with underlying liver disorders.
Skin and subcutaneous 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	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) which may occur within 48 hours of treatment start and may be bilateral	Rhabdomyolysis and/or Myopathy, Muscular weakness, Muscle tear, Muscle rupture, Ligament rupture, Arthritis
Renal and urinary disorders		Serum creatinine increased	Acute renal failure	Acute interstitial nephritis

Congenital, 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)

* Postmarketing experience

The drug may cause low blood sugar and mental health-related side effects. Low blood sugar levels, also called hypoglycaemia, can lead to coma. The mental health side effects more prominent and more consistent across the systemic fluoroquinolone drug class are as mentioned below;

- Disturbances in attention
- Disorientation
- Agitation
- Nervousness
- Memory impairment

Serious disturbances in mental abilities called delirium

Tinidazole
Reported side effects have generally been infrequent, mild and self-limiting.

The reported undesirable effects are listed below according to MedDRA system organ class classification and frequency. Within each frequency category, the ADRs are presented in the order of clinical importance. Frequency categories are expressed as: 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 (the frequency cannot be estimated from the available data).

System Organ Class	*Common*	*Not known*
Blood and the lymphatic system disorders		Leukopenia
Immune system disorders		Drug hypersensitivity
Metabolism and nutrition disorders	Decreased appetite	
Nervous system disorders	Headache	Convulsions Neuropathy peripheral Paraesthesia Hypoaesthesia Sensory disturbances Ataxia Dizziness Dysgeusia

Ear and labyrinth disorders	Vertigo	
Vascular disorders		Flushing
Gastrointestinal disorders	Vomiting Diarrhoea Nausea Abdominal pain	Glossitis Stomatitus Tongue discolouration
Skin and subcutaneous tissue disorders	Dermatitis allergic Pruritis	Angioedema Urticaria
Renal and urinary disorders		Chromaturia
General disorders and administration site conditions		Pyrexia Fatigue

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.

Tinidazole
In acute animal studies with mice and rats, the LD_{50} for mice was >3600mg/kg and >2300mg/kg for oral and intraperitoneal administration respectively. For rats, the LD_{50} was >2000mg/kg for both oral and intraperitoneal administration.
Signs and symptoms of overdosage: There are no reported overdoses in humans with Tinidazole.

Hepatotoxicity: Tinidazole is typically given for a few days only, but serum enzyme elevations have been reported with its use, and serum enzyme elevations during therapy is listed as a possible adverse event in the product label. Tinidazole is also capable of causing anaphylactic and allergic reactions including

urticaria, angioedema and bronchospasm, reactions which can be associated with minor serum enzyme elevations. Tinidazole, despite considerable use worldwide, has not been linked convincingly to instances of clinically apparent liver injury with jaundice.
Treatment for overdosage: There is no specific antidote for treatment of overdosage with Tinidazole. Treatment is symptomatic and supportive. Gastric lavage may be useful. Tinidazole is easily dialysable.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Ofloxacin
Pharmacotherapeutic group: Quinolone Antibacterials, Fluoroquinolones
ATC code: J01 MA 01

Tinidazole
Pharmacotherapeutic group: Antiinfectives for systemic use
ATC code: J 01XD02

Mechanism of Action

Ofloxacin
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.
The NCCLS MIC breakpoint recommendations are as follows:
S ≤ 2 mg/l and R ≥ 1 mg/l
Haemophilus influenzae and *Neisseria gonorrhoea* are exceptions with breakpoints at S ≤ 0.25 mg/l and R ≥ 1 mg/l
The BSAC general recommendations are S ≤ 2 mg/l and R ≥ 4 mg/l
According to DIN 58 940, the following limits apply for Ofloxacin:
S ≤ 1 mg/L, I = 2 mg/L, R ≥ 4 mg/L.
The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only an approximate guidance on probabilities whether micro-organisms will be susceptible to Ofloxacin or not.
Only those pathogens relevant to the indications are listed.

	European range of acquired bacterial resistance to Ofloxacin
Normally susceptible	
Aerobic Gram-positive micro organisms	
S. aureus - methicillin-sensitive	0.3-12.6%
S. pyogenes	2-5%
Aerobic Gram-negative micro organisms	

Acinetobacter spp	0.3-7.3%
Citrobacter spp.	3-15%
Enterobacter spp.	2-13%
E. coli	1-8%
H. influenzae	1%
Klebsiella spp.	1-10%
Moraxella spp.	0-0.2%
Morganella morganii	0-6.9%
N. gonorrhoeae	25%
Proteus spp.	1-15%
Serratia marcescens	2-2.4%
Others	
Chlamydia spp	
L. pneumophila	
Intermediately susceptible	
Aerobic Gram-positive micro organisms	
S. pneumoniae	70%
Providentia	17.1%
Aerobic Gram-negative micro organisms	
E. faecalis	50%
P. aeruginosa	20-30%
Serratia spp.	20-40%
Stenotrophomonas maltophilia	5.1-11%
Others	
Mycoplasma spp.	0-5.3%

Ureaplasma spp.	0-2.1%
Resistant	
Anaerobic bacteria	
S. aureus - methicillin-resistant	69.2-85.7%
T. pallidum	

Resistance
The main mechanism of bacterial resistance to Ofloxacin involves one or more mutations in the target enzymes, which generally confer resistance to other active substances in the class. Efflux pump and impermeability mechanisms of resistance have also been described and may confer variable resistance to active substances in other classes.

Tinidazole
Tinidazole is active against both protozoa and obligate anaerobic bacteria. The activity against protozoa involves *Trichomonas vaginalis*, *Entamoeba histolytica* and *Giardia lamblia.*
The mode of action of Tinidazole against anaerobic bacteria and protozoa involves penetration of the drug into the cell of the micro-organism and subsequent damage of DNA strands or inhibition of their synthesis.
Tinidazole is active against *Helicobacter pylori*, *Gardnerella vaginalis* and most anaerobic bacteria including *Bacteroides fragilis*, *Bacteroides melaninogenicus*, *Bacteroides spp.*, *Clostridium spp.*, *Eubacterium spp.*, *Fusobacterium spp.*, Peptococcus spp., *Peptostreptococcus spp.* and *Veillonella spp.*
Helicobacter pylori (H.pylori) is associated with acid peptic disease including duodenal ulcer and gastric ulcer in which about 95% and 80% of patients respectively are infected with this agent. *H.pylori* is also implicated as a major contributing factor in the development of gastritis and ulcer recurrence in such patients. Evidence suggests a causative link between *H.pylori* and gastric carcinoma.
Clinical evidence has shown that the combination of Tinidazole with omeprazole and clarithromycin eradicates 91-96% of *H.pylori* isolates.
Various different *H.pylori* eradication regimens have shown that eradication of *H.pylori* heals duodenal ulcers and reduces the risk of ulcer recurrence.

5.2 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 200mg averaged 2.6 µg/ml and was reached within one hour. The plasma elimination half-life was 5.7 to 7.0 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.

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

Tinidazole
Tinidazole is rapidly and completely absorbed following oral administration. In studies with healthy volunteers receiving 2g Tinidazole orally, peak serum levels of 40-51 micrograms/ml were achieved within two hours and decreased to between 11-19 micrograms/ml at 24 hours. Healthy volunteers who received 800mg and 1.6g Tinidazole IV over 10-15 minutes achieved peak plasma concentrations that ranged from 14 to 21mcg/ml for the 800mg dose and averaged 32mcg/ml for the 1.6g dose. At 24 hours post infusion, plasma levels of Tinidazole decreased to 4-5mcg/ml and 8.6mcg/ml respectively, justifying once daily dosing. Plasma levels decline slowly and Tinidazole can be detected in plasma at concentrations of up to 1 microgram/ml at 72 hours after oral administration. The plasma elimination half-life for Tinidazole is between 12-14 hours.

Tinidazole is widely distributed in all body tissues and also crosses the blood brain barrier, obtaining clinically effective concentrations in all tissues. The apparent volume of distribution is about 50 litres. About 12% of plasma Tinidazole is bound to plasma protein.

Tinidazole is excreted by the liver and kidneys. Studies in healthy patients have shown that over 5 days, 60-65% of an administered dose is excreted by the kidneys with 20-25% of the administered dose excreted as unchanged Tinidazole. Up to 5% of the administered dose is excreted in the faeces.

Studies in patients with renal failure (creatinine clearance <22ml/min) indicate that there is no statistically significant change in Tinidazole pharmacokinetic parameters in these patients.

5.3 Preclinical safety data
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 be investigated.

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.

Tinidazole has been shown to be mutagenic in some bacterial strains tested *in vitro* (with and without metabolic activation). Tinidazole was negative for mutagenicity in a mammalian cell culture system

utilising Chinese hamster lung V79 cells (HGPRT test system) and negative for genotoxicity in the Chinese hamster ovary (CHO) sister chromatid exchange assay. Tinidazole was positive for *in vivo* genotoxicity in the mouse micronucleus assay.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
Maize Starch, Sodium Starch Glycollate, Purified Talc, Magnesium Stearate
Film Coating:
Protectab HP-2

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

The caplets are provided in transparent PVC/Alu Blisters.
One carton contains 1 blister card of 10 caplets.

6.6 Special precautions for disposal and other handling

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/MANUFACTURER

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