FLOVID 200 TABLET

VIAZI04-1 (HK)

DESCRIPTION
9mm, round, bevel-edged, shallow convex with "FLOVID" embossed on one face and scored on another face, beige-coloured film-coated tablet.

COMPOSITION
Ofloxacin 200mg/ tablet.

ACTIONS AND PHARMACOLOGY
Ofloxacin is a broad-spectrum antibiotic. Being bactericidal, ofloxacin acts by inhibiting the resealing of DNA double-strands by the A subunits, and possibly the B subunits, of DNA gyrase following supercoiling. DNA gyrase is an essential bacterial enzyme, which is a critical catalyst in the duplication, transcription and repair of bacterial DNA.

PHARMACOKINETICS
Absorption
The administration of oral doses to fasting volunteers was followed by a rapid and almost complete absorption of ofloxacin. The peak plasma concentration after a single oral dose of 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.

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

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

Elimination
Excretion is primarily renal. Between 80 and 90% of the dose were recovered from the urine as unchanged substance. Ofloxacin was present in the bile in glucuronidised form. The pharmacokinetics of ofloxacin after intravenous infusion are very similar to those after oral doses. The plasma half-life is prolonged in persons with renal insufficiency; total and renal clearance decrease in accordance with the creatinine clearance. In renal insufficiency the dose should be reduced. No clinically relevant interactions were seen with food and no interaction was found between ofloxacin and theophylline.

INDICATIONS
Ofloxacin is indicated for the treatment of the following infections when caused by susceptible organisms: upper and lower urinary tract infections; lower respiratory tract infections; uncomplicated urethral and cervical gonorrhoea; non-gonococcal urethritis and cervicitis, skin and soft tissue infections.

CONTRAINDICATIONS
- This drug is contraindicated in patients who are allergic to ofloxacin or other quinolones and in patients with renal function impairment.
- Risk-benefit should be considered in patients with severe hepatic function impairment.
- Ofloxacin should not be used in patients with a past history of tendinitis.
- Ofloxacin is contra-indicated in patients with history of epilepsy or with a lowered seizure threshold.
- Ofloxacin is contra-indicated in children or growing adolescents, since animal experiments do not entirely exclude the risk of damage to the cartilage of joints in the growing subjects.

WARNINGS AND PRECAUTIONS
- Ofloxacin elimination is primarily through the kidneys; it is recommended that ofloxacin dosage be reduced in patients with impaired renal function.
- Patients with a history of hypersensitivity to quinolone antibacterials.
- Ofloxacin is not recommended for use during pregnancy because it has been shown to cause arthropathy in immature animals. Ofloxacin is excreted in breast milk in concentrations that are similar to those found in plasma. Therefore if ofloxacin must be given, breast-feeding is not recommended.
- Patients being treated with ofloxacin should not expose themselves unnecessarily to strong sunlight and should avoid UV rays (sun lamps, solaria).
- Caution is recommended if the drug is to be used in psychotic patients or in patients with a history of psychiatric disease.
- Administration of antibiotics, especially if prolonged, may lead to proliferation of resistant microorganisms. The patients condition must therefore be checked at regular intervals. If a secondary infection occurs, appropriate measures must be taken.
- Ofloxacin is not recommended for use in children or growing adolescents.
- Since elderly patients are more likely to have age-related decrease in renal function, they may require an adjustment of dosage. Careful monitoring is also required as side-effects may occur more frequently in the elderly.
- Cardiac disorders: Caution should be taken when using fluoroquinolones, including ofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:
  - congenital long QT syndrome
  - concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
  - uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
  - elderly
  - cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
- Exacerbation of Myasthenia Gravis: Fluoroquinolones, including ofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Post-marketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid ofloxacin in patients with a known history of myasthenia gravis.

PREGNANCY AND LACTATION
Not recommended in pregnancy and lactation.

MAIN SIDE/ADVERSE EFFECTS
- **Digestive and liver side effects**: ***Occasional:*** Nausea and vomiting, diarrhoea, abdominal pain, gastric symptoms. Diarrhoea may sometimes be a symptom of enterocolitis which may, in some cases, be haemorrhagic. ***Rare:*** Loss of appetite, increase in liver enzymes. ***Very rare:*** Cholestatic jaundice; hepatitis or severe liver damage may develop. A particular form of enterocolitis that can occur with antibiotics is pseudomembranous colitis (in most cases due to *Clostridium difficile*). Even if *Clostridium difficile* is only suspected, administration of ofloxacin should be discontinued immediately, and appropriate treatment given. Drugs that inhibit peristalsis should not be administered in such cases.
- **Central Nervous System**: ***Occasional:*** Headache, dizziness, sleep disorders, restlessness. ***Rare:*** Confusion, nightmares, anxiety, depression, hallucinations and psychotic reaction, drowsiness, unsteady gait and tremor (due to disorders of muscular coordination), neuropathy, numbness and paraesthesia or hypaesthesia, visual disturbances, disturbances of taste and smell, extrapyramidal symptoms. ***Very rare:*** Convulsion, hearing disorders (including, in exceptional cases, loss of hearing). ***Isolated cases:*** Psychotic reactions and depression with self-endangering behaviour including suicidal ideation or acts.
- **Cardiovascular Systems**: ***Occasional:*** Tachycardia, a temporary decrease in blood pressure. ***Rare:*** circulatory collapse.
- **Hematological side effects**: ***Very rare:*** anaemia, leucopenia (including agranulocytosis), trombocytopenia, pancytopenia. Only in some cases are these due to bone marrow depression. In very rare cases, haemolytic anaemia may develop.
- **Renal side effects:** ***Rare:*** Disturbances of kidney function. ***Isolated cases:*** Acute interstitial nephritis or an increase in serum creatinine, which may progress to acute renal failure.
- **Skin and allergic:** ***Occasional:*** Skin rash, itchy. ***Rare:*** Rash on exposure to excessive sunlight, hypersensitivity reactions, immediate or delayed, usually involving the skin (e.g. Erythema multiforme, Stevens-Johnson syndrome, vasculitis). In exceptional circumstance, vasculitis can lead to skin lesions including necrosis and may also involve internal organs. There are rarely other signs of anaphylaxis such as tachycardia, fever, dyspnoea, shock, angioneurotic oedema, vasculitis reactions, eosinophilia. In these cases, treatment should be discontinued immediately and where appropriate, supportive treatment given. ***Isolated cases:*** Pneumonitis

- **Other side effects:** ***Rare:*** Malaise. ***Very rare:*** Excessive rise or fall in blood-sugar levels. Weakness, joint and muscle pains (in exceptional cases these may be symptoms of rhabdomyolysis). ***Isolated cases:*** Tendon discomfort including inflammation and rupture of tendons (e.g. the Achilles tendon) particularly in patients treated concurrently with corticosteroids. In the event of signs of inflammation of a tendon, treatment with ofloxacin must be discontinued immediately and appropriate treatment must be initiated for the affected tendon. The possibility cannot be ruled out that ofloxacin may trigger an attack of porphyria in predisposed patients. Except in very rare instances (e.g. isolated cases of smell, taste and hearing disorders), the adverse effects observed subsided after discontinuation of ofloxacin.
- **Cardiac disorders:** Not known: ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged
- **Post marketing experience:** Exacerbation of myasthenia gravis

DRUG INTERACTIONS

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

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

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.

OVERDOSAGE

Clinical features: CNS toxicity, i.e. dizziness, drowsiness, mild to moderate disorientation, slurred speech as well as gastrointestinal reactions such as nausea and mucosal erosions.

Treatment for overdosage is symptomatic and supportive as there is no specific antidote. Ofloxacin is not efficiently removed by haemodialysis or peritoneal dialysis.

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.

Elimination of ofloxacin may be increased by forced diuresis.

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

DOSAGE AND ADMINISTRATION

- **General dosage recommendations:** The dose of ofloxacin is determined by the type and severity of the infection. The dosage range for adults is 200mg to 800mg daily. Up to 400mg may be given as a single dose, preferably in the morning, larger doses should be given as two divided doses. Generally, individual doses are to be given at approximately equal intervals. Flovid tablets should be swallowed with liquid; they should not be taken within two hours of magnesium/aluminium containing antacids, sucralfate or iron preparations since reduction of absorption of ofloxacin can occur.
  - *Lower urinary tract infection:* 200 to 400mg daily.
  - *Upper urinary tract infection:* 200 to 400mg daily increasing, if necessary, to 400mg twice a day.
  - *Lower respiratory tract infection:* 400mg daily increasing, if necessary, to 400mg twice daily.
  - *Uncomplicated urethral and cervical gonorrhoea:* A single dose of 400mg.
  - *Non-gonococcal urethritis and cervicitis:* 400mg daily in single or divided doses.
  - *Skin and soft tissue infections:* 400mg twice daily.
- **Impaired renal function:** Following a normal initial dose, dosage should be reduced in patients with impairment of renal function. When creatinine clearance is 20 – 50ml/minute (serum creatinine 1.5 – 5.0mg/dl) the dosage should be reduced by half (100 – 200mg daily). If creatinine clearance is less than 20ml/minute (serum creatinine greater than 5mg/dl) 100mg should be given every 24 hours. In patients undergoing haemodialysis or peritoneal dialysis, 100mg should be given every 24 hours.
- **Impaired liver function:** The excretion of ofloxacin may be reduced in patients with severe hepatic dysfunction.

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

Children: Ofloxacin is not indicated for use in children or growing adolescents.

Duration of treatment: Duration of treatment is dependent on the severity of the infection and the response to treatment. The usual treatment period is 5 - 10 days except in uncomplicated gonorrhoea, where a single dose is recommended.

Treatment should not exceed 2 months duration.

Note: The information given here is limited. For further information, consult your doctor or pharmacist.

Storage: Store below 30°C. Protect from light and moisture.

Presentation/Packing: Blisters of 1 x 10's, 10 x 10's.

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