FLOVID 200 TABLET

VIFLO06-var3 (SIN)

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.
Excipient: Colloidal Silicon Dioxide, Cornstarch, Lactose Monohydrate, Magnesium Stearate, Sodium Starch Glycolate, Hydroxypropyl Methylcelullose E-5, Hydroxypropyl Methylcelullose E-15, Iron Oxide Yellow, Isopropyl Alcohol, Propylene Glycol, Talc, Titanium Dioxide.

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
Ofloxacin is rapidly and well absorbed from the gastrointestinal tract with almost 100% oral bioavailability. Absorption may be delayed by the presence of food, but the extent of absorption is not substantially affected. The plasma half-life ranges from 5 to 8 hours; in renal impairment values of 15 to 60 hours have been reported.

About 25% bound to plasma proteins. Ofloxacin is widely distributed in body fluids, including the CSF and tissue penetration is good. It crosses placenta and is distributed into breast milk. Relatively high concentrations are achieved in bile.

There is limited metabolism to desmethyl and N-oxide metabolites; desmethylofloxacin has moderate antibacterial activity. Ofloxacin is eliminated mainly by the kidneys. Excretion is by tubular secretion and glomerular filtration and 75 to 80% of a dose is excreted unchanged in the urine over 24 to 48 hours, resulting in high urinary concentration. Less than 5% excreted in urine as metabolites. From 4 to 8% of a dose may be excreted in faeces.

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 contraindicated in patients with history of epilepsy or with a lowered seizure threshold.
- Ofloxacin is contraindicated 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.
- **Peripheral Neuropathy:** Cases of sensory or sensorimotor axonal polyneuropathy affecting small and / or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones, including Flovid. Symptoms may occur soon after initiation of Flovid and may be irreversible. Flovid should be discontinued immediately if the patient experiences symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense and vibratory sensation.
- **Vision disorders:** If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.
- **Disabling and potentially irreversible serious adverse reactions:** Fluoroquinolones, including ofloxacin, have been associated with disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. Commonly seen adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (hallucinations, anxiety, depression, insomnia, severe headaches, and confusion). Patients of any age or without pre-existing risk factors have experienced these adverse reactions. Discontinue ofloxacin immediately at the first signs or symptoms of any serious adverse reaction. In addition, avoid the use of fluoroquinolones, including ofloxacin, in patients who have experienced any of these serious adverse reactions associated with fluoroquinolones.
- **Aortic aneurysm or 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.
- **Psychiatric Adverse Reactions:** Fluoroquinolones, including ofloxacin, have been associated with an increased risk of psychiatric adverse reactions, including: toxic psychosis, hallucinations, or paranoia; depression or suicidal thoughts or acts; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These adverse reactions may occur following the first dose. If these reactions occur in patients receiving ofloxacin, discontinue ofloxacin immediately and institute appropriate measures.
- **Blood Glucose Disturbances:** As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with ofloxacin. In ofloxacin-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (for example, sulfonylurea) or with insulin. Severe cases of hypoglycaemia resulting in coma or death have been reported. In diabetic patients, careful monitoring of blood glucose is recommended. If a hypoglycaemic reaction occurs, discontinue ofloxacin and initiate appropriate therapy immediately.
- **Aortic aneurysm or dissection and heart valve regurgitation/incompetence:** Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake of fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones.

  Therefore, fluoroquinolones should only be used after a careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease or congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection or heart valve disease, or in presence of other risk factors or conditions predisposing:
  - for both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behçet´s disease, hypertension, rheumatoid arthritis) or additionally
  - for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or additionally
  - for heart valve regurgitation/incompetence (e.g. infective endocarditis).

  The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.

  In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

  Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

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), 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. Frequency not known: Peripheral neuropathy (that may be irreversible) and polyneuropathy.
- **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

- Concurrent use of ofloxacin with aluminium- and magnesium-containing antacids or ferrous sulfate, or sucralfate or zinc may reduce ofloxacin absorption by chelation, resulting in lower serum and urine concentrations of ofloxacin. For that reason, concurrent use is not recommended; ofloxacin should be taken at least 2 hours before or after any of these products.
- Concurrent use of ofloxacin with theophylline may reduce the hepatic metabolism and clearance of theophylline. There may be a further lowering of the cerebral seizure threshold when quinolones are given concurrently with other drugs which lower the seizure threshold, including theophylline and certain non-steroidal anti-inflammatory drugs.
- Prolongation of bleeding time has been reported during concomitant administration of ofloxacin and anticoagulants.
- Ofloxacin may cause a slight increase in serum concentrations of glibenclamide administered concurrently; patients treated with this combination should be closely monitored.
- Impairment of excretion and an increase in serum levels may occur when co-administered with other drugs that undergo renal tubular secretion (e.g. Probenecid, cimetidine, frusemide and methotrexate) with high doses of ofloxacin.
- 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 anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)

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:
Film-coated 200mg tablet in Alu-Alu blisters of 10 x 10's.

Product owner: HOVID Bhd.
121, Jalan Tunku Abdul Rahman,
30010 Ipoh, Perak, Malaysia.

Manufactured by: HOVID Bhd.
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