MEDOFLOXINE

Presentation
White, round, convex, film coated tablets with diameter of nucleus 9.5 mm

Pharmacology
Pharmacodynamics Ofloxacin is bactericidal and acts by inhibition of the A sub-unit of DNA gyrase (topoisomerase) which is an essential component in bacterial DNA reproduction.

Pharmacokinetics Ofloxacin is rapidly and well absorbed from the gastro-intestinal tract following oral administration. The oral bioavailability is close to 100% and peak plasma concentration of 3ug- 4ug/ml are achieved 1-2 hours post 400mg administration orally. Food may delay the rate of absorption but does not significantly affect the extent of absorption. Plasma half life ranges from 5 to 8 hours, this is prolonged in renal failure with values of 15 hours to 60 hours reported depending upon the extent of renal impairment.
Ofloxacin is about 25% plasma protein bound. It is widely distributed in body fluids, including the cerebrospinal fluid, and tissue penetration is good. Relatively high bile concentrations are reached.
It crosses the placenta and is excreted in breast milk.
Ofloxacin undergoes limited metabolism to desmethyl and N-oxide metabolites, with desmethyl ofloxacin having limited antimicrobial activity. The primary elimination route is via the kidney.
Excretion is by tubular secretion and glomerular filtration with 75% - 80% of a dose excreted unchanged in the urine over 24 – 48 hours. This results in high urinary concentrations. Less than 5% is excreted in the urine as metabolites and 4% - 8% may be excreted in the faeces.

Indications

The following indications are restricted to adults.
Ofloxacin is suitable for treatment of the following bacterial infections if these are caused by pathogens sensitive to ofloxacin:

- Acute pyelonephritis and complicated urinary tract infections
- Non-gonococcal urethritis and cervicitis
- Gonococcal urethritis and cervicitis due to susceptible *Neisseria gonorrhoeae*

In the following indications, ofloxacin should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections:

- Acute exacerbation of chronic obstructive pulmonary disease including bronchitis.*
- Cystitis.* Urethritis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

*Medofloxine should only be used:

- When Pseudomonas is considered AND patient is allergic to antipseudomonal penicillins/cephalosporins;
- For resistant organisms with no other alternative atibiotics available.

Dosage
The dose of ofloxacin is determined by the type and severity of the infection. The dosage range for adults is 200 mg to 800 mg daily.

Up to 400 mg may be given as a single dose, preferably in the morning. Generally, individual doses should be given at approximately equal intervals.

In individual cases it may be necessary to increase the dose to a maximum total dose of 800 mg daily, which should be given as 400 mg twice daily, at approximately equal intervals. This may be appropriate in infections due to pathogens known to have reduced or variable susceptibility to ofloxacin, in severe and/or complicated infections (e.g. of the respiratory or urinary tracts) or if the patient does not respond adequately.

The following doses are recommended:

Indications	*Single and Daily Doses*
Gonococcal urethritis and cervicitis due to susceptible *Neisseria gonorrhoeae*	400 mg

Uncomplicated cystitis	200 mg-400 mg daily
Acute pyelonephritis and complicated urinary tract infections	400 mg daily, increasing if necessary, to 400 mg twice a day
Non-gonococcal urethritis and cervicitis	400 mg daily

A single dose of 400 mg of ofloxacin is sufficient for the treatment of gonococcal urethritis and cervicitis due to susceptible *Neisseria gonorrhoeae*.

Impaired renal function

Following a normal initial dose, dosage should be reduced in patients with impairment of renal function as determined by creatinine clearance or plasma creatinine level.

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

* According to indication or dose interval

**The serum concentration of ofloxacin should be monitored in patients with severe renal impairment and ialysis patients.

Patients undergoing haemodialysis or peritoneal dialysis should be given 100 mg ofloxacin per day.
When creatinine clearance cannot be measured, it can be estimated with reference to the serum creatinine level using the following Cockcroft's formula for adults:

$$\text{Men: } \text{ClCr (ml/min)} = \frac{\text{weight(kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine (mg/dl)}}$$

or

$$\text{ClCr (ml/min)} = \frac{\text{weight(kg)} \times (140 - \text{age in years})}{0.814 \times \text{serum creatinine (µmol/l)}}$$

$$\text{Women: } \text{ClCr (ml/min)} = 0.85 \times (\text{above value})$$

Impaired liver function

The excretion of ofloxacin may be reduced in patients with severe hepatic dysfunction (e.g. cirrhosis of the liver with ascites). In such cases, it is recommended that the dose should not exceed 400 mg ofloxacin daily, because of possible reduction of excretion.

Elderly

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

Paediatric population

Ofloxacin is contraindicated for use in children or growing adolescents.

Duration

Treatment should not exceed 2 months duration.
A daily dose of up to 400 mg ofloxacin may be given as a single dose. In this case, it is preferable to administer ofloxacin in the morning.
Daily doses of more than 400 mg must be divided into two separate doses and be given at approximately equal intervals.

Method of administration

For oral use.
Ofloxacin tablets should be swallowed whole with sufficient liquid before or during meal times. They should not be taken within two hours of mineral antacids, sucralfate or metal ion preparations (aluminium, iron, magnesium or zinc), didanosine chewable or buffered tablets (for HIV), since reduction of absorption of ofloxacin can occur.

Contraindications
MEDOFLOXINE should not be used in patients with known hypersensitivity to ofloxacin or other quinolone-carboxylic acid derivatives.

MEDOFLOXINE is contraindicated in epileptics and in patients with pre-existing CNS lesions involving a lowered convulsions threshold eg: after cerebrocranial injuries, inflammations in the region of the CNS or stroke.

In children or adolescents in the growth phase and in pregnant or breast feeding women MEDOFLOXINE must not be used, because the safe use in such patients has not yet been sufficiently documented and judging from animal experiments, the risk of damage to the cartilage of joints in the growing organisms cannot be altogether excluded.

Warnings & Precautions
Patients who are being treated with MEDOFLOXINE should not expose themselves unnecessarily to strong sunlight and should avoid UV rays (sunray lamp, solarium).

The use of Ofloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using fluoroquinolones containing products (see section Adverse Effects/Undesirable Effects). Treatment of these patients with ofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.

Exacerbation of myasthenia gravis
Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in person with myasthenia gravis. Post marketing serious adverse events, including deaths and requirement for ventilator support have been associated with fluoroquinolones use in persons with myasthenia gravis. Avoid fluoroquinolones in patients with known history of myasthenia gravis.

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.

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 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 fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients (above 60 years of age), with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids in patients receiving daily doses of 1000 mg levofloxacin. Therefore, concomitant use of corticosteroids should be avoided.

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 and pharmacist 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 (see section Adverse Effects/Undesirable Effects).

Interactions With Other Medicaments
If cationic gastric antacids are taken at the same time, an attenuation of the MEDOFLOXINE effect must be taken into account.

Use in Pregnancy
MEDOFLOXINE should not be used in children, pregnant women and during lactation.

Effects on 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.

Adverse Reactions
Allergic manifestations may occur, in particular hypersensitivity reactions of the skin. In a few cases there have been fleabite-like haemorrhages (petechiae), the formation of blood blisters (haemorrhagic bullae) and small nodules (papules) with crust formation indicating vessel involvement (vasculitis). Rarely there have been symptoms such as facial oedema, swollen tongue, oedema of the glottis, tachycardia, dispnoea and shock, in some cases even after the first use. In such cases MEDOFLOXINE must be discontinued immediately and medical treatment eg shock therapy, initiated. There have been a few cases of skin reactions on exposure to strong sunlight.

There have been occasional disturbances of the nervous system, eg headaches, dizziness, sleep disturbances, vivid dreaming that may amount to nightmares, unsteady gait and tremor (disturbance of muscular coordination), numbness and tingling in the limbs (paraesthesiae), visual disturbances such as double vision and abnormal colour vision, disturbances of the sense of taste and smell, and hallucinations and psychotic reactions such as restlessness, agitation, anxiety and confusion.
These reactions have occurred in some patients even after the first use of MEDOFLOXINE. In such cases, MEDOFLOXINE must be discontinued immediately and the doctor must be notified. There have been rare reports of pain in joints and muscles.
There have been isolated cases of changes in the blood picture (leucopenia, agranulocytosis, thrombocytopenia, anaemia), transient increases in liver enzymes and/or bilirubin and renal function impairment eg; with a rise in serum creatinine.

Gastrointestinal symptoms may occur (gastric symptoms, abdominal pain, loss of appetite, nausea, vomiting, diarrhoea). If severe and persistent diarrhea occurs during or after therapy, the physician should be informed because in a few cases this may point to a serious intestinal disorder (pseudomembranous colitis) which requires immediate treatment. In such cases MEDOFLOXINE must be discontinued immediately and suitable therapy (eg: vancomycin oral, 4 x 250mg a day) initiated. Products inhibiting peristalsis are contraindicated.

Even when used as instructed, MEDOFLOXINE may alter reactivity to such an extent that the ability to drive vehicles or operate machinery may be impaired.

Experience to date has shown that the adverse reactions to MEDOFLOXINE treatment resolve on discontinuation of the preparation, except for very rare cases of taste and smell disorders. The physicians should always be informed of side effects that have been occurred.

Musculoskeletal and connective tissue disorders*
Nervous system disorders*
General disorders and administrative site conditions*
Psychiatric disorders*
Eye disorders*
Ear and labyrinth disorders*

*Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendinitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of fluoroquinolones in some cases irrespective of pre-existing risk factors (see section

Warnings and Precautions).

Exacerbation of myasthenia gravis
Post marketing Experience

Treatment of Overdose
Symptoms: Following acute overdosage the symptoms to be expected would be gastrointestinal reactions, such as nausea, vomiting and mucosal erosion.
Confusion, dizziness, consciousness impairment and seizures of a convulsion nature would also be anticipated.

Treatment: The prime objective, if possible within thirty minutes of overdose, is to remove unabsorbed ofloxacin. Administration of adsorbents, sodium sulphate and gastric lavage are advised. The gastric mucosa may be protected by the administration of anti-acids. Ofloxacin elimination can be enhanced by forced diuresis. Other treatment should be symptomatic and supportive.

Storage Conditions
Store below 30°C in the original package

Supply
Available in packs of 100's

Manufacturer
MEDOCHEMIE LTD
1-10, Constantinoupoleous Street, Limassol Cyprus

Product Registration Holder
KOMEDIC SDN BHD
4, Jalan PJS 11/14, Bandar Sunway 46150 Petaling Jaya

Date of Revision: 16/11/2021