For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

FLAVOSPAS-O

1. Generic Name

Flavoxate Hydrochloride and Ofloxacin Tablets

2. Qualitative and quantitative composition

Each film coated tablet contains:
Flavoxate Hydrochloride I.P……..200 mg
Ofloxacin I.P……..200 mg
Colour: Titanium Dioxide I.P.

The excipients used are Lactose, Microcrystalline Cellulose, Pregelatinised Starch, Sodium Starch Glycolate, Talc, Colloidal Silicon Dioxide, Magnesium Stearate, Methocel, Polyethylene Glycol, Titanium Dioxide.

3. Dosage form and strength

Film Coated Tablets
Strength - Flavoxate Hydrochloride - 200 mg, Ofloxacin - 200 mg

4. Clinical particulars

4.1 Therapeutic indication

Uncomplicated Urethritis and Cystitis Complicated UTIs: Cystitis secondary to Urinary tract and Spinal abnormalities Urethritis and Cystitis following Catheterization, Instrumentation and Surgical procedures UTI secondary to Pelvic Inflammatory Disease, Cervicitis, Vaginitis and Proctitis, Acute Prostatitis.

4.2 Posology and method of administration

Dose: As directed by the Physician

4.3 Contraindications

FLAVOSPAS-O is contraindicated in:

- Patients with known hypersensitivity to active substances, quinolones antibacterials or to any of the excipients of this product.
- Patients with Achalasia
- Patients with Urinary retention
- Patients with Glaucoma
- Myasthenia gravis
- Patients with a past history of tendinitis related to fluoroquinolone administration.
- Patients with a history of epilepsy or with a lowered seizure threshold.
- Children or growing adolescents and pregnant or breast-feeding women, since reported animal experiments do not entirely exclude the risk of damage to the cartilage of joints in the growing subject.
- Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents.

4.4 Special warnings and precautions for use

The use in children below the age of <12 years is not recommended.

The use of FLAVOSPAS-O 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.
Methicillin-resistant S. aureus are very likely to possess co-resistance to fluoroquinolones, including ofloxacin. Therefore, FLAVOSPAS-O 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).

Escherichia coli infection
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. Ofloxacin is not the drug of first choice for pneumonia caused by Pneumococci or Mycoplasma or infection caused by β-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 (urethral gonococcal infection, pelvic inflammatory disease and epididymo-orchitis), 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.

Pelvic inflammatory disease
For pelvic inflammatory disease, ofloxacin should only be considered in combination with anaerobe coverage.

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.

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.

Clostridium difficile-associated disease
Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with ofloxacin (including several weeks after treatment), may be symptomatic of pseudo- membranous colitis (CDAD). CDAD may range in severity from mild to life threatening, the most severe form 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-membranous colitis is suspected, ofloxacin must be stopped immediately.

Appropriate specific antibiotic therapy must be started without delay (e.g. oral vancomycin, oral teicoplanin or metronidazole). Products inhibiting the peristalsis are contraindicated in this clinical situation.

Patients predisposed to seizures
Quinolones may lower the seizure threshold and may trigger seizures. Ofloxacin is contraindicated in patients with a history of epilepsy and, as with other quinolones, ofloxacin should be used with extreme caution in patients predisposed to seizures.

Such patients may be patients with pre-existing central nervous system lesions, concomitant treatment with fenbufen and similar non-steroidal anti-inflammatory drugs or with drugs which lower the cerebral seizure threshold, such as theophylline.

In case of convulsive seizures, treatment with ofloxacin should be discontinued

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 tendinitis 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.

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.

Patients with renal impairment
Since active substances are mainly excreted by the kidneys, the dose of FLAVOSPAS-O should be adjusted and caution is therefore required in patients with renal impairment.

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:
• 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)
• cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
• 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.

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.

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 behaviour including suicide attempt, sometimes after a single dose. 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, pruritis 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

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

Superinfection
As with other antibiotics, the use of ofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's

condition is essential. If secondary infection occurs during therapy, appropriate measures should be taken.

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.

Dysglycaemia
As with all quinolones, disturbances in blood glucose, including both hyperglycaemia and hypoglycaemia 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.

Vision disorders
If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

Interference with laboratory tests
In patients treated with ofloxacin, determination of opiates in urine may give false-positive results. It may be necessary to confirm positive opiate screens by more specific method.

Patients with rare hereditary disorders
Patients with rare hereditary disorders of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Drugs interactions

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).

Antacids, Sucralfate, Metal Cations
Co-administered magnesium/aluminium antacids, sucralfate, zinc or iron preparations can reduce absorption. Therefore, ofloxacin should be taken 2 hours before such preparations.

Prolongation of bleeding time has been reported during concomitant administration of FLAVOSPAS-O and anticoagulants.

Theophylline, fenbufen or similar non-steroidal antiinflammatory drugs
No pharmacokinetic interactions of ofloxacin were found with theophylline in a reported 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.

In case of convulsive seizures, treatment with ofloxacin should be discontinued.

Glibenclamide
Ofloxacin may cause a slight increase in serum concentrations of glibenclamide administered concurrently; patients treated with this combination should be closely monitored.

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.

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 be monitored in patients treated with vitamin K antagonists because of a possible increase in the effect of coumarin derivatives.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy
Based on a limited amount of reported human data, the use of FLAVOSPAS-O in the first trimester of pregnancy has not been associated with an increased risk of major malformations or other adverse effects on pregnancy outcome. Reported animal studies of ofloxacin have shown damage to the joint cartilage in immature animals but no teratogenic effects. Therefore, FLAVOSPAS-O should not be used during pregnancy.

Breast-feeding
Ofloxacin is excreted into human breast milk in small amounts while it is unknown whether flavoxate (metabolites) is excreted in human milk. Because of the potential for arthropathy and other serious toxicity in the nursing infant, breast-feeding should be discontinued during treatment with ofloxacin.

4.7 Effects on ability to drive and use machines
Since there have been occasional reports of somnolence, impairment of skills, dizziness and visual disturbances, patients should know how they react to FLAVOSPAS-O before they drive or operate machinery. These effects may be enhanced by alcohol.

4.8 Undesirable effects
The source of the below ADRs frequencies is represented by data reported through clinical trials, observational studies, and spontaneous reporting.

System organ class	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 (cannot be estimated from available data)**
Infections and infestations		Fungal infection,			

System organ class	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 (cannot be estimated from available data)**
		Pathogen resistance			
Blood and the lymphatic system disorders				Anaemia Haemolytic anaemia, Leukopenia, Eosinophilia, Thrombocytopenia	Agranulocytosis Bone marrow failure
Immune system disorders			Anaphylactic reaction**, Anaphylactoid reaction**, Angioedema**	Anaphylactic shock**, Anaphylactoid shock**	Hypersensitivity
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	Tremor Dyskinesia Ageusia Syncope Benign intracranial hypertension

System organ class	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 (cannot be estimated from available data)**
				symptoms or other disorders of muscular coordination	(Pseudotumor cerebri).
Eye disorders*		Eye irritation, Visual impairment	Visual disturbance		Uveitis Glaucoma
Ear and labyrinth disorders*		Vertigo		Tinnitus, Hearing loss	Hearing impaired
Cardiac disorders			Tachycardia		Ventricular arrhythmias, torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged, Palpitations
Vascular disorders			Hypotension		
Respiratory, thoracic and mediastinal disorders		Cough, Nasopharyngitis	Dyspnoea, Bronchospasm		Allergic pneumonitis, Severe dyspnoea
Gastro-intestinal disorders	Nausea	Abdominal pain, Dry mouth, Diarrhea, Vomiting, Dyspepsia	Enterocolitis, sometimes haemorrhagic	Pseudo-membranous colitis* Jaundice cholestatic	Flatulence Constipation Pancreatitis
Hepato-bilary disorders			Hepatic enzymes increased (ALAT, ASAT, LDH, gamma-GT and/or		Jaundice, Hepatitis, which may be severe**; Severe liver injury, including cases

System organ class	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 (cannot be estimated from available data)**
			alkaline phosphatase) Blood bilirubin increased		of acute liver failure, sometimes fatal, have been reported 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 generalized 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			Urinary retention, Serum creatinine increased	Acute renal failure	Acute interstitial nephritis
Congenital and familial/genetic disorders					Attacks of porphyria in patients with porphyria
General disorders and administration					Asthenia Pyrexia

System organ class	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 (cannot be estimated from available data)**
site conditions*					Pain (including pain in the back, chest and extremities)

*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 tendonitis, 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 quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors.

** postmarketing experience.

- **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose

The most important signs to be expected following acute overdosage are CNS symptoms such as confusion, dizziness, impairment of consciousness and seizures, increases 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 reported post marketing experience.

In the case of overdose, steps to remove any unabsorbed FLAVOSPAS-O e.g. gastric lavage, administration of adsorbents and sodium sulphate, if possible during the first 30 minutes, are recommended; antacids are recommended for protection of the gastric mucosa. A fraction of FLAVOSPAS-O 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 FLAVOSPAS-O 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.

5. Pharmacological properties

5.1 Mechanism of Action

Flavoxate

The mechanism of action involves intracellular cyclic AMP accumulation and calcium blocking activity. It inhibits bladder contractions induced by various agonists or by electrical stimulation and inhibits the frequency of bladder voiding contractions. It increases bladder volume capacity, reduces the threshold and micturition pressure.

Ofloxacin

Ofloxacin is a quinolone-carboxylic acid derivative with a wide range of antibacterial activity against both gram negative and gram positive organisms. It is active after oral administration.

The primary mode of action of the quinolones is the specific inhibition of bacterial DNA gyrase. This enzyme is required for DNA replication, transcription, repair and recombination. Its inhibition leads to expansion and destabilisation of the bacterial DNA and hence to cell death.

It appears that certain quinolones, including ofloxacin, have a second non RNA dependent action on bacterial cells, which enhances bactericidal effectiveness. The nature of this second action has not yet been clarified.

5.2 Pharmacodynamic properties

Flavoxate

Pharmacotherapeutic group: Urinary antispasmodics
ATC code: G04BD02

Flavoxate hydrochloride (and its main metabolite methyl flavone carboxylic acid, MFCA) is an antispasmodic selective to the urinary tract. In reported animal and human studies, flavoxate hydrochloride has been shown to have a direct antispasmodic action on smooth muscle fibres..

Ofloxacin

Pharmacotherapeutic group: Quinolone antibacterials, Fluoroquinolones
ATC code: J01M A01

PK/PD relationship

Fluoroquinolones have a concentration-dependent bactericidal activity, with a moderate post antibiotic effect. For this class of antimicrobials, the ratio between AUC and MIC or Cmax and MIC is predictive of clinical success.

Mechanisms of resistance

Resistance to ofloxacin is acquired through a stepwise process by target site mutations in both type II topoisomerases, DNA gyrase and topoisomerase IV. Other resistance mechanisms such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may also affect susceptibility to ofloxacin

Susceptibility testing breakpoints

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains.

Breakpoints set by EUCAST:

MIC breakpoint (mg/L)		
Microorganism	**Susceptible ≤**	**Resistant >**
Enterobacteriaceae	0.5	1
Staphylococcus spp.	1	1[a]
Streptococcus pneumoniae[b]	0.125	4
Haemophilus influenzae	0.5	0.5
Moraxella catarrhalis	0.5	0.5
Neisseria gonorrheae	0.125	0.25

a. Breakpoints relate to high dose therapy

b. Wild type *S. pneumonia* are not considered susceptible to ofloxacin and are therefore categorized as intermediate

Susceptibility
The prevalence of resistance may vary geographically and over time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species, including microorganisms with intermediate susceptibility
AerobicGram-positivemicro-organisms *Bacillus anthracis Bordetella pertussis* Corynebacteria *Streptococci*
AerobicGram-negativemicro-organisms Campylobacter Enterobacter *Haemophilus influenzae Legionella pneumophila Moraxella catarrhalis Morganella morganii Proteus vulgaris* Salmonella Shigella Yersinia
Othermicro-organisms Chlamydia *Chlamydophila pneumonia Mycoplasma hominis Mycoplasma pneumoniae Ureaplasma urealyticum*
Species for which acquired resistance may be a problem
AerobicGram-positivemicro-organisms *Staphylococci coagulase negative Staphylococcus aureus (methicillin-sensitive) Streptococcus pneumoniae*
AerobicGram-negativemicro-organisms *Acinetobacter baumannii Citrobacter freundii Escherichia coli Klebsiella oxytoca Klebsiella pneumoniae Neisseria gonorrhoeae Proteus mirabilis Pseudomonas aeruginosa* Serratia
Inherently resistant organisms
AerobicGram-positivemicro-organisms Enterococci *Listeria monocytogenes* Nocardia Staphylococci methi-R
Anaerobicmicro-organisms Bacteroides spp. *Clostridium difficile*

Therapeutic doses of ofloxacin are devoid of pharmacological effects on the voluntary or autonomic nervous systems.

5.3 Pharmacokinetic properties

Flavoxate
Reported oral studies in man have indicated that flavoxate is readily absorbed from the intestine and converted, to a large extent, almost immediately to MFCA.

As per reported data, following an IV dose (equimolar to 100 mg), the following parameters were calculated for flavoxate: T½ 83.3 mins: apparent volume of distribution 2.89 l/kg. The apparent distribution of MFCA was 0.20 l/kg. No free flavoxate was found in urine (24 hours). However, 47% of the dose was excreted as MFCA.

Following single oral dosing to volunteers of 200 mg and 400 mg flavoxate, almost no free flavoxate was detected in the plasma. The peak level of MFCA was attained at 30-60 mins after the 200 mg dose and at around two hours following the 400 mg dose. The

AUC for the 400 mg dose was approximately twice as large as the AUC for the 200 mg dose. About 50% of the dose was excreted as MFCA within 12 hours; most being excreted within the first 6 hours.

After repeated oral dosing (200 mg, TDS, 7 days) the cumulative excretion of metabolites stabilised at 60% of the dose on the third day remaining almost unchanged after one week

Ofloxacin

Ofloxacin is almost completely absorbed after oral administration. The peak serum concentration, after a single dose of 200 mg, averages 2.5 to 3µg/ml within one hour. The serum elimination half-life is 6-7 hours and is linear. The apparent volume of distribution is 120 litres. Following multiple dosing, the serum concentration is not significantly increased (multiplication factor approximately 1.5). Ofloxacin concentrations in the urine and at the site of urinary tract infections exceed those measured in serum by 5 to 100- fold. Ofloxacin is primarily excreted unchanged in the urine.

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.

6. Nonclinical properties

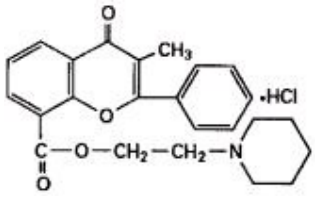
6.1 Animal Toxicology or Pharmacology

Reported non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and toxicity to reproduction and development. Carcinogenicity studies have not been performed.

7. Description

Flavoxate hydrochloride

Flavoxate hydrochloride is a synthetic urinary tract spasmolytic. Chemically, flavoxate hydrochloride is 2-piperidinoethyl 3-methyl-4-oxo-2-phenyl-4 H-1-benzopyran-8-carboxylate hydrochloride. The empirical formula of flavoxate hydrochloride is $C_{24}H_{25}NO_4$•HCl. The molecular weight is 427.94. The chemical structure is:

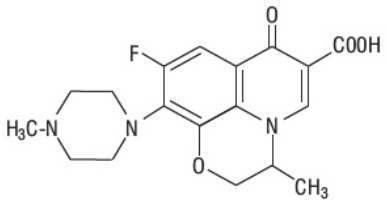


Flavoxate hydrochloride is a white to almost white crystalline powder which is slightly soluble in ethanol (95 percent) and in water; sparingly soluble in dichloromethane.

Ofloxacin

Ofloxacin tablets are a synthetic broad-spectrum antimicrobial agent for oral administration. Chemically, ofloxacin, USP, a fluorinated carboxyquinolone, is the racemate, (±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-

pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid having chemical formula is $C_{18}H_{20}FN_3O_4$ and molecular weight is 361.4. The chemical structure is:



Ofloxacin is pale yellow to bright yellow crystalline powder which is soluble in glacial acetic acid, slightly soluble in water, dichloromethane and methanol.

Flavoxate Hydrochloride and Ofloxacin Tablets are white capsule shaped film coated tablets. The excipients used are Lactose, Microcrystalline Cellulose, Pregelatinised Starch, Sodium Starch Glycolate, Talc, Colloidal Silicon Dioxide, Magnesium Stearate, Methocel, Polyethylene Glycol, Titanium Dioxide.

8. Pharmaceutical particulars

8.1 Incompatibilities
None Stated

8.2 Shelf-life
Do not use later than date of expiry

8.3 Packaging information
FLAVOSPAS-O is packed in blister strips of 10 tablets.

8.4 Storage and handing instructions
Store in a cool, dry place. Protect from light.

9. Patient Counselling Information

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet:

9.1 What FLAVOSPAS-O is and what it is used for.

FLAVOSPAS-O is a combination of Flavoxate Hydrochloride and Ofloxacin.
Flavoxate belong to a group of medicines which relieve and prevent muscle spasms and Ofloxacin is an antibiotic which works by killing bacteria that cause infections.

FLAVOSPAS-O is used for treatment of Uncomplicated Urethritis and Cystitis Complicated UTIs: Cystitis secondary to Urinary tract and Spinal abnormalities Urethritis and Cystitis following Catheterization, Instrumentation and Surgical procedures UTI secondary to Pelvic Inflammatory Disease, Cervicitis, Vaginitis and Proctitis, Acute Prostatitis.

9.2 What you need to know before you use FLAVOSPAS-O.

Do not use FLAVOSPAS-O if:

- You are allergic to flavoxate hydrochloride, ofloxacin or to any of the other ingredients of this medicine.
  Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of the lips, face, throat and tongue.
- You have ever had swelling of the tendons (called tendinitis) which can affect areas such as the wrist or the achilles tendon
- You have epilepsy or are at risk of fits You have a problem with your red blood cells known as ‘glucose-6-dehydrogenase deficiency’
- You are pregnant or breast-feeding (see ‘Pregnancy and breast-feeding’ section below)
- You are under 18 years of age or are still growing
- If you have a gastrointestinal disease that affects the normal passage of food (obstruction);
- If you have an gastro-intestinal bleeding
- If you have a muscular inability to swallow (achalasia)
- If you are not able to completely empty your bladder (urinary retention)

- If you are being treated for an eye disease called glaucoma
- If you have a disease which causes general weakness and fatigability of the muscles (myasthenia gravis)

Do not take this medicine if the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking FLAVOSPAS-O.

Warnings and precautions
You should not take fluoroquinolone/quinolone antibacterial medicines, including FLAVOSPAS-O, if you have experienced any serious adverse reaction in the past when taking a quinolone or fluoroquinolone. In this situation, you should inform your doctor as soon as possible

Talk to your doctor or pharmacist before taking FLAVOSPAS-O:
- if you have liver or kidney problems
- You have heart disease or problems with your heartbeat
- You have received a transplantation
- You have nerve problems (peripheral neuropathy)
- You are taking medicines that can affect your heart (see section Taking other medicines)
- You were born with or have family history of prolonged QT interval (seen on ECG, electrical recording of the heart)
- You have a salt imbalance in the blood (especially low levels of potassium or magnesium in the blood)
- You have a very slow heart rhythm (called 'bradycardia')
- You have a weak heart (heart failure)
- You have a history of heart attack (myocardial infarction)
- You are female or elderly
- You are taking other medicines that result in abnormal ECG changes (see section Taking other medicines)
- You have or have ever had any mental health problems
- You suffer from a condition called myasthenia gravis, which causes muscle weakness and excessive muscle fatigue
- You have been told by your doctor that you cannot tolerate some sugars.
- You have been diagnosed with an enlargement or 'bulge' of a large blood vessel (aortic aneurysm or large vessel peripheral aneurysm)
- You have experienced a previous episode of aortic dissection (a tear in the aorta wall)
- You have a family history of aortic aneurysm or aortic dissection or other risk factors or predisposing conditions (e.g. connective tissue disorders such as Marfan syndrome or vascular Ehlers-Danlos syndrome, or vascular disorders such as Takayasu arteritis, giant cell arteritis, Behcet's disease, high blood pressure, or known atherosclerosis)

If you feel sudden, severe pain in your abdomen, chest or back, go immediately to an emergency room. If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking this medicine.

There have been very rare reports of potentially life-threatening skin rashes (Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis) with the use of FLAVOSPAS-O tablets. Symptoms of which may include: flu-like symptoms followed by a painful red or purplish rash that spreads and blisters. If you develop any of the above you must stop

taking your medicine and inform your doctor straight away. FLAVOSPAS-O tablets are not recommended if you have a suspected MRSA infection.

While being treated with FLAVOSPAS-O tablets, avoid strong sunlight and do not use sun lamps or solariums, as your skin may be more sensitive to light.

If you experience pain in your fingers or toes whilst being treated with FLAVOSPAS-O tablets, tell your doctor or nurse immediately.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking FLAVOSPAS-O tablets.

When taking this medicine
Pain and swelling in the joints and inflammation or rupture of tendons may occur rarely. Your risk is increased if you are elderly (above 60 years of age), have received an organ transplant, have kidney problems or if you are being treated with corticosteroids. Inflammation and ruptures of tendons may occur within the first 48 hours of treatment and even up to several months after stopping of FLAVOSPAS-O therapy. At the first sign of pain or inflammation of a tendon (for example in your ankle, wrist, elbow, shoulder or knee), stop taking FLAVOSPAS-O, contact your doctor and rest the painful area. Avoid any unnecessary exercise as this might increase the risk of a tendon rupture.

You may rarely experience symptoms of nerve damage (neuropathy) such as pain, burning, tingling, numbness and/or weakness especially in the feet and legs or hands and arms. If this happens, stop taking FLAVOSPAS-O and inform your doctor immediately in order to prevent the development of potentially irreversible condition.

Prolonged, disabling and potentially irreversible serious side effects
Fluoroquinolone/quinolone antibacterial medicines, including FLAVOSPAS-O, have been associated with very rare but serious side effects, some of them being long lasting (continuing months or years), disabling or potentially irreversible. This includes tendon, muscle and joint pain of the upper and lower limbs, difficulty in walking, abnormal sensations such as pins and needles, tingling, tickling, numbness or burning (paraesthesia), sensory disorders including impairment of vision, taste and smell, and hearing, depression, memory impairment, severe fatigue, and severe sleep disorders.

If you experience any of these side effects after taking FLAVOSPAS-O, contact your doctor immediately prior to continuing treatment. You and your doctor will decide on continuing the treatment considering also an antibiotic from another class.

Other medicines and FLAVOSPAS-O
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because FLAVOSPAS-O can affect the way some other medicines work. Also some medicines can affect the way FLAVOSPAS-O works.

In particular, tell your doctor if you are taking the following:

- Medicines to thin the blood such as warfarin
- Methotrexate used for rheumatism or cancer

Other medicines that can alter your heart rhythm:

- • Medicines that belong to the group of antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide)
- Tricyclic antidepressants

- Some antimicrobials (that belong to the group of macrolides)
- Some antipsychotics

The following medicines can change the way FLAVOSPAS-O tablets work or FLAVOSPAS-O tablets may change the way some of these medicines work:

• Medicines used to stop your blood from clotting

• Medicines used for high blood pressure

• Medicines that contain iron (for anaemia) or zinc

• Medicines that help put you to sleep (anaesthetics)

• Water tablets (diuretics) such as furosemide

• Antacids that contain magnesium or aluminium - used for indigestion

• Glibenclamide - used for diabetes

• Probecenid - used for gout

• Cimetidine - used for stomach ulcers or indigestion

• Sucralfate - used for stomach ulcers

The following medicines, when taken with FLAVOSPAS-O tablets, can increase the chance of you getting side effects:

- Other antibiotics (such as erythromycin, azithromycin or clarithromycin)
- Medicines for depression (such as amitriptyline, clomipramine or imipramine)
- Theophylline – used for breathing problems
- Medicines used to control your heartbeat (such as amiodarone, quinidine, procainamide, or disopyramide)
- Non steroidal anti-inflammatory drugs (NSAIDs) – used for pain relief and inflammation (such as ibuprofen, diclofenac or indometacin)
- Corticosteroids - used for inflammation
- Antipsychotics - used to treat psychiatric disorders such as schizophrenia and bipolar disorder.

Children
FLAVOSPAS-O should not be used in children younger than 12 years of age.

Taking FLAVOSPAS-O tablets with food and drink
Do not drink alcohol while taking FLAVOSPAS-O tablets. This is because it may make you feel dizzy or sleepy.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
You may feel sleepy or dizzy or have problems with your eyesight while taking this medicine. If you experience any of these effects don't drive or use machinery.

9.3 How to use FLAVOSPAS-O

Always take FLAVOSPAS-O exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Carefully read the label from the pharmacist. Ask your pharmacist if you are not sure about the dose to take. The medicine should be taken for the prescribed number of days.

Taking this medicine
• Take this medicine by mouth
• Swallow the tablets whole with a drink of water
• The tablets should be taken after a meal in order to prevent nausea
• When taking FLAVOSPAS-O tablets, avoid strong sunlight and do not use sun lamps or solaria
• Medicines containing iron (for anaemia), antacids (for indigestion or heartburn) or sucralfate (for stomach ulcers) should be avoided for two hours before or after taking FLAVOSPAS-O Tablets
• If you feel the effect of your medicine is too weak or strong, do not change the dose yourself, but ask your doctor
• When taking FLAVOSPAS-O tablets, if your eyesight becomes impaired or if your eyes seem to be otherwise affected, consult an eye specialist immediately.

When to take your medicine
• The length of your treatment will depend on how serious your infection is
• Treatment should not be longer than 2 months
• Higher doses should be taken in two doses, one in the morning and one in the evening

Kidney or liver problems
If you have any kidney or liver problems you may be given a lower dose.

Children and Adolescents:
This medicine should not be given to children or adolescents.

Urine Tests
Taking FLAVOSPAS-O tablets may affect the results of some urine tests. If you are going to have a urine test, it is important to tell your doctor you are taking FLAVOSPAS-O tablets.

If you take more FLAVOSPAS-O than you should
If you have too much of this medicine, talk to your doctor straightaway. Take the medicine pack with you. This is so the doctor knows what you have taken. The following effects may happen: feeling confused or dizzy, loss of consciousness, fits, feeling sick or blood in your stools.

If you forget to take FLAVOSPAS-O
If you forget to take a dose, take it as soon as you remember. However, if it is nearly time for the next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking FLAVOSPAS-O
Do not stop taking this medicine without talking to your doctor. You should not stop taking FLAVOSPAS-O just because you feel better. This is because the infection may come back or get worse again.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible Side Effects

Like all medicines, these suspension can cause side effects, although not everybody gets them.

Stop taking FLAVOSPAS-O tablets and see a doctor or go to a hospital straight away if:

• You have an allergic reaction. The signs may include a rash, joint pain, swallowing or breathing problems, swelling of your lips, face, throat or tongue

Stop taking FLAVOSPAS-O tablets and see a doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:

Very Rare (affects less than 1 in 10,000 people)

• An uneven or fast heartbeat, you may also feel faint

• Watery diarrhoea, which may have blood in it, possibly with stomach cramps and a high temperature

• Fits

• Hearing problems or hearing loss

• Liver problems that may cause your eyes or skin to go yellow (jaundice)

• Severe skin rashes (Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis) which may include blistering or peeling of the skin around the lips, eyes, mouth, nose and genitals. Symptoms may include flu-like symptoms followed by a painful red or purplish rash that spreads and blisters. If you develop any of the above you must stop taking this medicine and inform your doctor straight away

• Skin rashes caused by strong sunlight

• Feeling faint, light-headed or dizzy, due to low blood pressure

• Muscle weakness, joint and muscle pains

• Feeling weak or irritable, sweating and/or trembling. This could be due to lowering of blood sugar levels

• Feeling thirsty and passing water more often than usual. This could be due to a raise in blood sugar levels

• Swelling or discomfort in your tendons, such as in the achilles tendon

• Severe inflammation of the kidneys, which may result in your kidneys stopping working. Signs may include a rash, high temperature and general aches and pains

• Severe depression or mental illness. Some people who are depressed think of harming or killing themselves

• Very rare cases of long lasting (up to months or years) or permanent adverse drug reactions, such as tendon inflammations, tendon rupture, joint pain, pain in the limbs, difficulty in walking, abnormal sensations such as pins and needles, tingling, tickling, burning, numbness or pain (neuropathy), depression, fatigue, sleep disorders, memory impairment, as well as impairment of hearing, vision, and taste and smell have been associated with administration of quinolone and fluoroquinolone antibiotics, in some cases irrespective of pre-existing risk factors.

Rare (affects less than 1 in 1000 people)

• Numbness or tingling in the hands and feet or being very sensitive to touch

• Hives, pruritus

• Inability to completely empty the bladder (urinary retention)

• Fatigue

Frequency Unknown

• Abnormal fast heart rhythm

• Life-threatening irregular heart rhythm

• Alteration of the heart rhythm (called 'prolongation of QT interval', seen on ECG, electrical activity of the heart)

• Indigestion, flatulence (passing wind), constipation

• Fever, pain (back, chest, limbs)

• Severe abdominal pain (pancreatitis)

• Impaired hearing

• Inflammation of the eye (uveitis)

• Skin redness with extensive scaling (exfoliative dermatitis)

• Loss of appetite, skin and eyes becoming yellow in colour, dark-coloured urine,

itching, or tender stomach (abdomen). These may be signs of liver problems which may include a fatal failure of the liver

• Liver problems

• Problems with eyesight

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days:

Uncommon (affects less than 1 in 100 people)
• Feeling sick (nausea), being sick (vomiting), dryness of mouth, gastric pain and upset stomach (dyspepsia)
• Headaches, sleeping problems, feeling dizzy or restless
• Skin rash or itching

Rare (affects less than 1 in 1000 people)
• Loss of appetite

• Feeling confused or anxious, nightmares, seeing things that are not there, depression and mental illness, feeling drowsy, trembling, problems walking due to poor muscle control

• Changes in eyesight

• Changes in or loss of your sense of taste or smell

• Changes in levels of liver enzymes shown in blood tests

• A general feeling of being unwell

Very Rare (affects less than 1 in10,000 people)

• Feeling tired, faint, dizzy and having pale skin. These could be signs of anaemia

• You may bruise more easily than usual. This could be because of a blood problem called 'thrombocytopenia'

• Cough or shortness of breath, caused by lung inflammation

Not known (frequency cannot be estimated from the available data)

• Persistent headache with or without blurred vision (benign intracranial hypertension)

• Hypersensitivity, anaphylactic reaction, anaphylactic shock

• Confusional state

• Glaucoma

• Fast or irregular heartbeats (called palpitations)

• Yellowing of the skin and eyes (Jaundice), liver disorders, abnormal results of liver function tests (hepatic enzyme abnormal)

• Redness (of the skin).

It is possible that FLAVOSPAS-O may trigger an attack of porphyria (a rare illness which affects the metabolism) in some patients.

Tell your doctor if any of the side effects gets serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.
By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store FLAVOSPAS-O
Store in a cool, dry place. Protect from light.

9.6 Contents of the pack and other information

What FLAVOSPAS-O contains:

The active substance in this product is Flavoxate Hydrochloride and Ofloxacin.

The other ingredients are Lactose, Microcrystalline Cellulose, Pregelatinised Starch, Sodium Starch Glycolate, Talc, Colloidal Silicon Dioxide, Magnesium Stearate, Methocel, Polyethylene Glycol, Titanium Dioxide.

10. Details of manufacturer
Manufactured in India by:
Windlas Healthcare (P) Limited.
Plot no.183 & 192,
Mohabewala Industrial Area,
Dehradun- 248 110, Uttarakhand.

11. Details of permission or licence number with date
Mfg Lic No. 47/UA/2009 issued on 03/09/2020

12. Date of revision
Dec 2020

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/FLAVOSPAS-O 200mg,200mg/DEC-2020/04/PI