1.3.1 The Summary of Product Characteristics (SmPC)

1- Name of the Medicinal Product:

1.1 Product Name

- Generic Name or International Non-Proprietary Name (INN)

Ofloxacin Tablets USP 400 mg

1.2 Dosage Strength

Each Film Coated Tablet Contains:

Ofloxacin USP…….400 mg

Excipients……. q. s

Colour: -Titanium Dioxide

1.3 Dosage Form

Film Coated Tablet

2- Quality and Quantitative Composition:

2.1 Qualitative Declaration

Each Film Coated Tablet Contains:

Ofloxacin USP…….400 mg

Excipients……. q. s

Colour: -Titanium Dioxide

2.2 Quantitative Declaration

Description: White, Capsule shape, coated tablets having one side break line and other side plain.

MODULE 1

STD Batch Size: 285.200 kg / 4.00 Lac Tablets

Reference. MFR No: MFR/T-E428, Version No: 00

Sr. No	Ingredients	A.R No.	Specification	Quantity/ Tablet in mg	Standard Qty in kg
Part I-Mixing					
1	Ofloxacin	RM190901	USP	403.000	161.200
Part-II Paste Preparation					
2	P.V.P-K 30	RM196060	BP	15.000	6.000
3	Isopropyl Alcohol	RM19212	BP	q.s.	q.s.
Part II Mixing					
4	Maize Starch	RM197821	BP	75.000	30.000
5	Microcrystalline Cellulose Powder	RM191970	BP	65.000	26.000
6	Dibasic Calcium Phosphate	RM192136	BP	93.500	37.400
7	Sodium Starch Glycolate	RM194000	BP	10.000	4.000
Part II Paste Preparation					
8	Maize Starch	RM196068	BP	12.000	4.800
9	P.V.P-K 30	RM191510	BP	3.000	1.200
10	Methyl Paraben	RM198110	BP	1.000	0.400
11	Propyl Paraben	RM192611	BP	0.500	0.200
12	Purified Water	WP92013	BP	q.s.	q.s.
Lubrication					
13	Magnesium Stearate	RM198222	BP	6.000	2.400
14	Talcum	RM191615	BP	4.000	1.600
15	Sodium Starch Glycolate	RM194030	BP	15.000	6.000
16	Sodium Lauryl Sulphate	RM192850	BP	10.000	4.000
Coating					
17	Colour Titanium Dioxide	RM192920	BP	17.500	7.000
18	Isopropyl Alcohol	RM19214	BP	q.s.	q.s.
19	Methylene Chloride	RM19241	BP	q.s.	q.s.
Average Weight Of Tablet 730.500 mg					

Note:

Active material was calculated on assay or Potency Basis.

BP = British Pharmacopoeia

USP = United States Pharmacopoeia

MODEL 1

❖ ***Justification for addition of Preservative***

1. Justification for addition of Preservative such as Methyl Paraben in the preparation of Binder Salutation.
2. All the raw material are analyst as per Pharmacopeial Specification for chemical & Microbial Limit test.
3. Purified Water used for the manufacturing is under monitoring program for Microbial Limit test.
4. Manufacturing area monitored as per the predefined frequency for environmental monitoring.
5. As an additional precaution Methyl Paraben added in the preparation binder solution to take care of Microbial Purity.

1. Quantity Adjusted to 100 % API assay

Calculation:

*Quantity of Ofloxacin USP to be dispensed on 100% assay on as is basis.

Ofloxacin USP 400 mg Assay Claimed as 100% Please refer attached Raw Material COA.

MODULE 1

3. Pharmaceutical Form

White, Capsule shape, Film coated tablets having one side break line and other side plain.

4. Clinical particulars

4.1 Therapeutic indications

The following indications are restricted to adults.

Ofloxacin is suitable for treatment of the following 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 exacerbations of chronic obstructive pulmonary disease, including chronic bronchitis
- Community-acquired pneumonia
- Uncomplicated cystitis
- Urethritis

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

MODULE 1

4.2 Posology and method of administration

Posology

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
Community-acquired pneumonia. Acute exacerbations of chronic obstructive pulmonary disease including bronchitis.	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*.

Special patient populations

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

MODULE 1

<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 dialysis 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:

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

or

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

Women: $ClCr\ (ml/min) =$ 0.85 x (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 see section 4.4 QT interval prolongation).

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.

MODULE 1

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

4.3 Contraindications

The use of ofloxacin is contraindicated as follows:

• Hypersensitivity to the active substance, to any other fluoroquinolone antibacterials, or to any of the excipients listed in.

• In patients with a history of epilepsy or an existing central nervous system disorder with a lowered seizure threshold.

• In patients with a history of tendon disorders related to fluoroquinolone administration

• In children or growing adolescents, and in pregnant or breastfeeding women, since animal experiments do not entirely exclude the risk of damage to the growth-plate cartilage in the growing organism cannot be entirely excluded.

• In patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity because they may be prone to haemolytic reactions when treated with quinolone antibacterial agents.

4.4 Special warnings and precautions for use

The use of ofloxacin 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

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

MODULE 1

Methicillin-resistant S. aureus

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

Resistance to fluoroquinolones of E. coli

The most common pathogen involved in urinary tract infections varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in *E. coli* to fluoroquinolones.

***Streptococcus pneumoniae*, β-haemolytic Streptococci and Mycoplasma**

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 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.

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.

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

MODULE 1

(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.

Aortic aneurysm and 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 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 aortic 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, Behcet'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.

Severe bullous reactions

Cases of severe bullous skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with ofloxacin (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

MODULE 1

Diseases caused by Clostridioides difficile

Diarrhoea, especially if severe, persistent and/or bloody, occurring during or after treatment with ofloxacin (including several weeks after treatment), may be symptomatic of pseudomembranous colitis (*Clostridioides difficile* – associated diarrhoea – CDAD*)*. CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis It is therefore important to consider this diagnosis in patients who develop serious diarrhoea during or after treatment with ofloxacin. If pseudomembraneous colitis is suspected, treatment with ofloxacin should be discontinued immediately.

Specific targeted antibiotic therapy must be started without delay (e.g. oral vancomycin, oral teicoplanin or metronidazole). Products that inhibit 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 or with a known predisposition to seizures and, as with other quinolones, ofloxacin should be used with extreme caution in patients predisposed to seizures.

Patients with a known predisposition to seizures may include those with pre-existing central nervous system lesions, concomitant treatment with fenbufen and similar non-steroidal anti-inflammatory drugs (NSAIDs), or with drugs which lower the cerebral seizure threshold, such as theophylline.

In case of convulsive seizures, treatment with ofloxacin should be discontinued (see section 4.5).

Tendonitis and tendon rupture

Tendonitis 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 tendonitis 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. The daily dose should be adjusted in elderly patients based on creatinine clearance Close monitoring of these patients is therefore necessary if they are prescribed ofloxacin.

MODULE 1

All patients should consult their physician if they experience symptoms of tendonitis. At the first sign of tendonitis (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 tendonopathy occur.

Patients with impaired renal function

Since ofloxacin is mainly excreted by the kidneys, the dose of ofloxacin should be adjusted in patients with renal impairment.

Patients with history of psychotic disorder

Psychotic reactions have been reported in patients receiving fluoroquinolones, including ofloxacin. In some cases these have progressed to suicidal ideation or self-endangering behavior including suicide attempt, sometimes after a single dose of ofloxacin (see section 4.8). In the event that a patient develops these reactions, ofloxacin should be discontinued immediately at the first signs or symptoms of these reactions and patients should be advised to contact their prescriber for advice.

Alternative non-fluoroquinolone antibacterial therapy should be considered, and appropriate measures instituted.

Ofloxacin should be used with caution in patients with a history of psychotic disorder or in patients with psychiatric disease.

Patients with impaired liver function

Ofloxacin should be used with caution in patients with impaired liver function, as liver damage may occur. Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with fluoroquinolones. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen

Patients treated with vitamin K antagonists

Due to possible increase in coagulation tests (PT [prothrombin time]/INR [International Normalised Ratio]) and/or bleeding in patients treated with fluoroquinolones, including ofloxacin, in

MODULE 1

combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomitantly

Myasthenia gravis

Fluoroquinolones, including ofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Postmarketing serious adverse reactions, including deaths and the requirement for respiratory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Ofloxacin is not recommended in patients with a known history of myasthenia gravis.

Superinfection

As with other antibiotics, the use of ofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms. Especially Enterococci, resistant strains of some organisms or Candida. Repeated evaluation of the patient's condition is essential and periodic *in vitro* susceptibility tests may be useful. If secondary infection occurs during therapy, appropriate measures should be taken.

Prevention of photosensitisation

Photsensitisation has been reported with ofloxacin It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), during treatment and for 48 hours following treatment discontinuation in order to prevent photosensitisation.

QT interval prolongation

Very rare cases of QT interval 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:

- elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including ofloxacin, in these populations.
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- 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)

MODULE 1

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

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported more frequently in the elderly 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 diabetic patients, careful monitoring of blood glucose is recommended

Ofloxacin treatment should be stopped immediately if a patient reports disturbance in blood glucose, and alternative non-fluoroquinolone antibacterial therapy should be considered.

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.

Patients with glucose-6-phosphate-dehydrogenase deficiency

Patients with latent or diagnosed glucose-6-phosphate-dehydrogenase deficiency may be predisposed to haemolytic reactions if they are treated with quinolones. Therefore if ofloxacin has to be used in these patients, potential occurrence of haemolysis should be monitored.

Interference with laboratory tests

In patients treated with ofloxacin, determination of opiates or porphyrin levels in urine may give false-positive results. It may be necessary to confirm positive opiate or porphyrin screens by more specific methods.

Cross-resistance with various quinolones has been shown.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an ophthalmologist should be consulted immediately.

MODULE 1

Excipient with known effect

Ofloxacin contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Ofloxacin contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids, Sucralfate, Metal Cations

Co-administered magnesium/aluminum antacids, sucralfate, zinc or iron preparations and didanosine chewable/buffered tablets can reduce absorption of ofloxacin. Therefore, ofloxacin should be taken 2 hours before such preparations.

Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs

No pharmacokinetic interactions of ofloxacin were found with theophylline in a clinical study. However, a pronounced lowering of the cerebral seizure threshold may occur when quinolones are given concurrently with theophylline, nonsteroidal anti-inflammatory drugs, or other agents, which lower the seizure threshold.

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

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 co-administered 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) (see section 4.4 QT interval prolongation).

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).

MODULE 1

Coagulation tests should, therefore, be monitored in patients treated with vitamin K antagonists because of a possible increase in the effect of coumarin derivatives (see section 4.4).

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

Ofloxacin is excreted into human breast milk in small amounts. Because of the potential for arthropathy and other serious toxicity in the nursing infant, breast-feeding should be discontinued during treatment with ofloxacin

4.7 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.

4.8 Undesirable effects

The information given below is based on data from clinical studies and on extensive post marketing experience.

MODULE 1

System organ class	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very rare (< 1/10,000)**	**Not known (cannot be estimated from available data)***
Infections and infestations	Overgrowth of non-susceptible microorganisms incl. Fungi			
Blood and lymphatic system disorders			Anaemia, Haemolytic anaemia, Leucopenia, Eosinophilia, Thrombocytopenia	Agranulocytosis, Bone marrow failure, Pancytopenia
Immune system disorders		Anaphylactic reaction**, Anaphylactoid reaction**, Angioedema**	Anaphylactic shock**, Anaphylactoid shock**	
Metabolism and Nutrition disorders		Anorexia, Hypoglycaemic coma		Hypoglycaemia in diabetics treated with hypoglycaemic agents Hyperglycaemia,
Psychiatric disorders*	Agitation, Sleep disorder, Insomnia	Psychotic disorder (e.g. hallucination), Anxiety, Confusional state, Nightmares, Depression, Delirium		Psychotic disorder and depression with self-endangering behaviour including suicidal ideation or suicide attempt Nervousness
Nervous system disorders*	Dizziness, Headache	Somnolence, Paraesthesia, Dysgeusia, Parosmia, Memory impairment	Peripheral sensory neuropathy**, Peripheral sensory motor neuropathy**, Convulsion**, Extra-pyramidal symptoms or other disorders of muscular	Tremor, Dykinesia, Ageusia, Syncope, Benign intracranial hypertension (Pseudotumor cerebri)

MODULE 1

			coordination	
Eye disorders*	Eye irritation	Visual disturbance		Uveitis
Ear and labyrinth disorders*	Vertigo		Tinnitus, Hearing loss	Hearing impaired
Cardiac disorders		Tachycardia		Ventricular arrhythmias and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged
Vascular disorders***		Hypotension		
Respiratory, thoracic and mediastinal disorders	Cough, Nasopharyngitis	Dyspnoea, Bronchospasm		Allergic pneumonitis (pneumonia), Severe dyspnoea
Gastrointestinal disorders	Abdominal pain, Diarrhoea, Nausea, Vomiting	Enterocolitis, sometimes haemorrhagic	Pseudo-membranous colitis**	Dyspepsia, Flatulence, Constipation, Pancreatitis
Hepatobiliary disorders		Hepatic enzymes increased (ALT, AST, LDH, gamma-GT and/or alkaline phosphatase), Blood bilirubin increased	Jaundice cholestatic	Hepatitis, which may be severe, ** Severe liver injury, including cases of acute liver failure, sometimes fatal, have been reported with ofloxacin, primarily in patients with underlying liver disorders

MODULE 1

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 (vasculitis presents generally with petechiae, bleeding vesicles and small pimples with scabs and may even affect internal organs).	Stevens-Johnson syndrome, Acute generalised exanthemous pustulosis, Drug rash, Stomatitis, Exfoliative dermatitis
Musculoskeletal and connective tissue disorders*		Tendonitis	Arthralgia, Myalgia, Tendon rupture (e.g. Achilles tendon) as is the case with fluoroquinolones, this effect may occur within 48 hours of treatment start and may be bilateral	Rhabdomyolysis and/or Myopathy, Muscular weakness, Muscle tear, Muscle rupture, Ligament rupture, Arthritis
Renal and urinary disorders		Serum creatinine increased	Acute renal failure	Acute interstitial nephritis
Congenital, familial and genetic disorders				Attacks of porphyria in patients with porphyria
General disorders and administration site conditions*				Asthenia, Pyrexia, Pain (including pain in back, chest and extremities)

MODULE 1

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

** Postmarketing experience

***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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

The most important signs to be expected following acute overdose are CNS symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures increases in QT interval as well as gastrointestinal reactions such as nausea and mucosal erosions.

CNS effects including confusional state, convulsion, hallucination, and tremor have been observed in post marketing experience.

Management

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

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

MODULE 1

protection of gastric mucosa. A fraction of ofloxacin may be removed from the body with haemodialysis. Peritoneal dialysis and CAPD are not effective in removing ofloxacin from the body. No specific antidote exists.

Elimination of ofloxacin may be increased by forced diuresis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

Mechanism of action

This medicinal product contains ofloxacin, a broad-spectrum anti-infective agent that belongs to the fluoroquinolones group. Ofloxacin acts on both Gram-positive and Gram-negative bacteria.

Resistance

Resistance to ofloxacin is acquired in a multi-step process at the target site through mutations in the two type II topoisomerases, DNA gyrase and topoisomerase IV. Other mechanisms of resistance such as permeability barriers (common in Pseudomonas aeruginosa) and efflux systems may also influence susceptibility to ofloxacin.

The prevalence of resistance may vary based on geographical and temporal data for a given species. It is recommended that information about local resistance be obtained, in particular for the treatment of serious infections. If necessary, the opinion of an expert can be requested when the local prevalence of resistance is such that the usefulness of the product is uncertain, at least for certain types of infections.

Susceptibility testing breakpoints

Minimum Inhibitory Concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Organisms	**Minimum inhibitory Concentration (mg/l)**	
	Susceptible	**resistant**
Enterobacterales	≤ 0.25	> 0.5
Haemophilus influenzae	≤ 0.06	> 0.06
Moraxella catarrhalis	≤ 0.25	> 0.25
Neisseria gonorrhoeae	≤ 0.125	> 0.25

PK-PD relationship

Fluoroquinolones have a dose-dependent bactericidal activity with a moderate post-antibiotic effect. For this class of antibiotics, the ratio between the area under the curve (AUC) and the minimum inhibitory concentration (MIC) or between the maximum concentration (Cmax) and the MIC is predictive of clinical success.

Bacteriological activity

The following pathogens may be considered susceptible:

- *Methicillin-susceptible Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *Neisseria gonorrhoeae*
- *Neisseria meningitidis*
- *Haemophilus influenzae*
- *Escherichia coli*
- *Klebsiella*
- *Enterobacter, Citrobacter*
- *Proteus (indole-negative and indole-positive)*
- *Salmonella, Shigella*
- *Yersinia enterocolitica*
- *Campylobacter jejuni*
- *Vibrio cholerae*
- *Vibrio parahaemolyticus*
- *Hafnia spp.*
- *Aeromonas spp.*
- *Plesiomonas spp.*
- *Chlamydiae*
- *Legionella pneumophila.*

Moderately susceptible bacteria include:

- *Serratia marcescens*
- *Enterococcus faecium*
- *Clostridium tetani*

MODULE 1

- *Enterococci*
- *Streptococcus pyogenes*
- *Streptococcus pneumoniae*
- *Pseudomonas aeruginosa*
- *Acinetobacter*
- *Mycoplasma pneumoniae*
- *Streptococcus viridans*
- *Mycoplasma hominis*
- *Mycobacterium tuberculosis*
- *Mycobacterium fortuitum.*

Bacteria that can be considered resistant:

- *Fusobacterium spp.*
- *Eubacterium spp.*
- *Peptococci*
- *Peptostreptococci*
- *Treponema pallidum*
- *Clostridium difficile*
- *Nocardia asteroids*
- *Bacteroides spp.*
- *Ureaplasma urealyticum.*

In the case of urinary tract infection, an MIC < 16 µg/mL can still be considered susceptible.
Therapeutic doses of ofloxacin are devoid of pharmacological effects on the voluntary or autonomic nervous system.

5.2 Pharmacokinetic properties

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 200 mg averaged

MODULE 1

2.6 µg/ml and was reached within one hour. The plasma elimination half-life was 5.7 to 7 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-desmethyl-ofloxacin 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.

5.3 Preclinical safety data

Preclinical effects in conventional studies of safety pharmacology, acute toxicity, repeated dose toxicity, reproductive studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Joint toxicity was observed at exposure in the human therapeutic range in juvenile rats and dogs. Ofloxacin exhibits a neurotoxic potential and causes reversible testicular alterations at high doses.

Mutagenicity studies showed no evidence for mutagenicity of ofloxacin. However, like some other quinolones Ofloxacin is phototoxic in animals at exposure in the human therapeutic range. The phototoxic, photomutagenic and photocarcinogenic potential of ofloxacin is comparable with that of other gyrase inhibitors.

MODULE 1

Preclinical data from conventional genotoxicity studies reveal no special hazard to humans, carcinogen potential has not been investigated.

Reproduction toxicity

Ofloxacin has no effect on fertility, peri- or postnatal development, and therapeutic doses did not lead to any teratogenic or other embryotoxic effects in animals. Ofloxacin crosses the placenta and levels reached in the amniotic fluid are about 30% of the maximal concentrations measured in maternal serum.

6. Pharmaceutical Particulars:

6.1 List of excipients

- P.V.P-K 30
- Isopropyl Alcohol
- Microcrystalline Cellulose Powder
- Dibasic Calcium Phosphate
- Maize Starch
- Methyl Paraben
- Propyl Paraben
- Purified Water
- Magnesium Stearate
- Talcum
- Sodium Starch Glycolate
- Sodium Lauryl Sulphate
- Colour Titanium Dioxide
- Methylene Chloride

6.2 Incompatibilities

None stated

6.3 Shelf life

3 Years from the date of manufacture.

MODULE 1

6.4 Special precautions for storage

Store below 30°C.

Protect from light and moisture.

6.5 Nature and contents of container

Pack 10 Tablets in a blister with the help of printed aluminium foil and Aluminium base foil in the arrangement of 1x10's. Pack such 1 blister in one Pre-Printed carton in the arrangement of 1x10 along with Leaflet. Pack such 10 Printed inner carton in a printed outer carton in the arrangement of 10x1x10's.

7- Marketing Authorization Holder:

SURMOUNT LABORATORIES PVT. LTD.

Plot No A-2/4003, GIDC Ind. Estate,

Ankleshwar-393002, Gujarat, India

Email: surmountlaborat@gmail.com

8- Marketing Authorization Number (s):

To be allocated.

9.0 Date of first authorization / renewal of authorization

To be allocated

10.0 Date of revision of the text

To be allocated

MODULE 1