Brand Name : **AGONOR TABLETS** **Generic Name** : Norfloxacin Tablets BP 400 mg		2021
Module 1 **1.5**	Administrative Information and Product Information Product Information	**Confidential**

1.5 PRODUCT INFORMATION

1.5.1 Prescribing information (Summary of products characteristics)

SUMMARY PRODUCT CHARACTERISTICS

1. Name of drug product:

AGONOR TABLETS (Norfloxacin Tablets BP 400 mg)

2. Qualitative and Quantitative Composition:

Each film coated tablet contains: Norfloxacin BP 400 mg

3. Pharmaceutical form:

White coloured, elongated, film coated tablets having “Breakline” on one side and other side “Plain” of each tablets.

4. Clinical particulars:

4.1 Therapeutic indications

Norfloxacin is a broad-spectrum bactericidal/chemotherapeutic agent, indicated for the treatment of the following infections caused by Norfloxacin-susceptible gram-positive and gram-negative aerobic bacteria:

- Uncomplicated acute cystitis. In uncomplicated cystitis Norfloxacin should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.
- Urethritis including cases due to susceptible *Neisseria gonorrhoeae*
- Complicated urinary tract infections (except complicated pyelonephritis)
- Complicated acute cystitis
  Consideration should be given to an official local guidance, e.g. national recommendations regarding the appropriate use and prescription of antibacterial agents.

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4.2 Posology and method of administration

The dosage depends on the susceptibility of the pathogens and severity of the disease; see recommended dosage in the table below. Oral Norfloxacin containing products are not recommended for the treatment of acute or chronic complicated pyelonephritis Susceptibility of the causative organism to the treatment should be tested (if possible), although therapy may be initiated before the results are available.

In case of suspected failure of therapy, microbiological investigation for possible bacterial resistance should be undertaken.
Dosage in adults

Diagnosis	Dosage	Therapy duration
uncomplicated acute cystitis3	400 mg twice daily	3 days
urinary tract infections (urethritis, including cases due to susceptible *Neisseria gonorrhoeae*)	400 mg twice daily	7-10 days
Complicated urinary tract infections: urethritis and acute cystitis	400 mg twice daily	2 - 3 weeks

Symptoms accompanying urinary tract infections such as burning on passing water or fever and pain subside after only one to two days. Nevertheless, the recommended length of treatment should be fully adhered to
Prolonged therapy should be guided by evaluation of response of the patient taking into account official therapeutic guidelines and assessment of the risk of development of resistance.
This condition is considered to be met in women.

Dosage for patients with renal insufficiency
Norfloxacin is suitable for treatment of patients with renal insufficiency. In patients with severe impaired renal function, the advantages and disadvantages of the use of Norfloxacin should be carefully weighed up in each individual case. For patients with a creatinine clearance ≤ 30 ml/min x 1.73 m2 the recommended dosage is one Norfloxacin BP 400 mg daily.
At this dosage, fluid and tissue concentrations exceed the MlCs of most Norfloxacin-susceptible pathogens responsible for urinary tract infections.

Dosage for elderly patients
Pharmacokinetic studies have shown no evidence of differences in Norfloxacin pharmacokinetics in elderly patients, apart from a slight prolongation of half-life. In the absence of renal impairment no adjustment of dosage is necessary for elderly patients.

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Pediatric population

Norfloxacin is not recommended for use in children or growing adolescents

Method of administration

The film-coated tablets should be swallowed with sufficient fluid (e.g. a glass of water) at least one hour before or two hours after a meal or ingestion of milk

The film-coated tablets should preferably be taken in the morning and evening. If only one dose is to be administered daily, this should always be taken at the same time of the day.

4.3 Contraindications

Hypersensitivity to any component of this product tablets or any chemically related quinolone antibacterial or to any of the other excipients listed in section 6.1.
Norfloxacin is contraindicated in patients with a history of tendinitis and/or tendon rupture related to Fluoroquinolone administration.

Use in children

Norfloxacin BP 400mg is contra-indicated in prepubertal children and growing adolescents.
As with other quinolones, Norfloxacin BP 400 mg has been shown to cause arthropathy in immature animals. The safety of Norfloxacin BP 400 mg in children has not been adequately explored and therefore the use of Norfloxacin in prepubertal children or growing adolescents is contra-indicated

Use in pregnancy and lactation and in children and growing adolescents

Norfloxacin must not be used by children and growing adolescents or by pregnant and lactating women. This is because safety has not yet been sufficiently established for these groups of patients

4.4 Special warnings and precautions for use

The use of Norfloxacin 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 Norfloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.

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 Fluoroquinolone irrespective of their age and pre-existing risk factors. Norfloxacin 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.

Photosensitivity

Photosensitivity may occur in patients taking Norfloxacin tablets or other quinolone-type drugs. Longer periods of exposure to the sun and stronger sunlight should be avoided during treatment. In the same way the use of solarium should be denied during this time. Treatment should be stopped if symptoms of photosensitivity occur.

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Tendinitis and/or 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 Fluoroquinolone 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 Norfloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilization). Corticosteroids should not be used if signs of tendinopathy occur.

Use in patients with epilepsy and other CNS disorders

In the case of epileptics and patients with existing CNS disorders (e.g. a low convulsive threshold, a history of convulsions, reduced cerebral blood flow, changes to brain structure or stroke), Norfloxacin should only be given if the benefit clearly outweighs the risk, because of the possibility of CNS side effects in these patients. Convulsions have been reported in rare cases in patients receiving Norfloxacin. Norfloxacin may lead to exacerbations and aggravation of the symptoms in patients with known or suspected psychiatric disorders, hallucinations and/or confusion. The usually appropriate emergency measures are indicated (e.g. keeping airways free, administer anticonvulsants).

Impaired renal function

In patients with severely impaired renal function, the advantages and disadvantages of use of Norfloxacin tablets should be carefully weighed up in each individual case (see section 4.2). As the renal function is reduced by age particularly elderly belong to this group of patients. The urinary concentration of Norfloxacin may be reduced if renal function is severely impaired since elimination of Norfloxacin occurs predominantly by the renal route.

Crystalluria

In case of prolonged treatment, the occurrence of crystalluria should be monitored. While crystalluria is not expected to occur under normal conditions with dosage regimen 400 mg twice daily, as a precaution, the daily recommended dosage should not be exceeded and the intake of sufficient fluids should be guaranteed to ensure proper state of hydration and adequate urinary output.

Myasthenia gravis

Norfloxacin can exacerbate the symptoms of myasthenia gravis which may result in life threatening weakness of respiratory muscles. Adequate counter measures should be taken at any sing of respiratory distress.

In patients treated with Norfloxacin, unmasking or exacerbation of myasthenia gravis has been reported. As this may include potentially life-threatening respiratory failure, patients with myasthenia gravis should be advised to immediately seek medical treatment if exacerbation of symptoms occurs.

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Vision disorders

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

Pseudomembranous colitis

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including Norfloxacin, and may range in severity from mild to life-threatening. Therefore it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Studies indicate that a toxin produced by Clostridium difficile is a primary cause of "antibiotic-associated colitis". If Clostridium difficile associated diarrhea (CDAD) is suspected or confirmed, ongoing antibiotic use not directed against C. difficile should be discontinued and appropriate therapy instituted immediately. Anti-peristaltic drugs are contraindicated in this situation.

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity (anaphylactic or anaphylactoid) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. In such cases, therapy with Norfloxacin must be discontinued immediately and appropriate emergency action must be started (e.g. antihistamines, glucocorticosteroids, sympathomimetics and ventilation if necessary).

Cardiac disorders

Caution should be taken when using Fluoroquinolone, including Norfloxacin 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 Norfloxacin, in these populations.

Aortic aneurysm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of Fluoroquinolone particularly in the older population.
Therefore, Fluoroquinolone 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.

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Peripheral neuropathy.
Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysaesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with Norfloxacin 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 hypoglycaemia and hyperglycaemia have been reported (see section 4.8), 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.

4.5 Interaction with other medicinal products and other forms of interaction
Quinolones, including Norfloxacin, have been shown in vitro to inhibit CYP1A2. Concomitant use with drugs metabolized by CYP1A2 (e.g. caffeine, clozapine, ropinirole, theophylline, tizanidine) may result in increased levels of these drugs, with the potential risk of increased toxicity. Patients taking any concomitant drugs metabolized by CYP1A2 should be carefully monitored

Theophylline
Elevated plasma concentrations of theophylline have been reported during concomitant use of theophylline and quinolones. Adverse reactions caused by theophylline have also been reported sporadically during concomitant use of Norfloxacin and theophylline. The theopylline concentration in plasma should thus be monitored and the dosage of theopylline adjusted if necessary.

Cyclosporine
Elevated serum concentrations of ciclosporine have been reported with concomitant use of Norfloxacin. Cicloporine serum levels should be monitored and appropriate ciclosporin dosage adjustments made when these drugs are used concomitantly.

Warfarin
Quinolones, including Norfloxacin, may enhance the effects of oral anticoagulants, including warfarin or its derivatives or similar agents. When concomitant administration of these products cannot be avoided, measurements of prothrombin time or other suitable coagulation tests should be carried out.

Glibenclamide
The concomitant administration of quinolones including Norfloxacin with glibenclamide (a sulphonylurea agent) has, on rare occasions, resulted in severe hypoglycaemia. Therefore monitoring of blood glucose is recommended when these agents are co-administered.

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Probenecid
Co-administration of probenecid does not affect serum concentrations of Norfloxacin, but urinary excretion of the drug diminishes.

Nitrofurantoin
As with other organic acid antibacterials, antagonism has been demonstrated in vitro between Norfloxacin and nitrofurantoin. Concomitant use of Norfloxacin and nitrofurantoin should therefore be avoided.

Multivitamins, products containing iron or zinc, antacids or sucralfate
Multivitamins, products containing iron or zinc, antacids or sucralfate should not be administered concomitantly with, or within 2 hours of, the administration of Norfloxacin, because they may interfere with absorption, resulting in lower serum and urine levels of Norfloxacin.

Didanosine
Products containing didanosine should not be administered concomitantly with, or within 2 hours of, the administration of Norfloxacin, because the products may interfere with absorption resulting in lower serum and urine levels of Norfloxacin.

Caffeine
Some quinolones, including Norfloxacin, have also been shown to inhibit the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its half-life that may lead to accumulation of caffeine in plasma when products containing caffeine are consumed while taking Norfloxacin.

Non-steroidal anti-inflammatory drug (NSAID)
The concomitant administration of a non-steroidal anti-inflammatory drug (NSAID) with a quinolone, including Norfloxacin, may increase the risk of CNS stimulation and convulsive seizures. Therefore Norfloxacin should be used with caution in individuals receiving NSAIDs concomitantly.

Fenbufen
Animal data have shown that quinolones in combination with fenbufen can lead to convulsions. Therefore, concomitant administration of quinolones and fenbufen should be avoided.

Mycophenolic acid
Lowered bioavailability of mycophenolic acid was observed in healthy volunteers receiving combined treatment with Norfloxacin and metronidazole.

Miscellaneous preparations (preparations containing iron or antacids, products containing magnesium, aluminium, calcium or zinc)
Calcium preparations, multivitamin preparations, preparations containing iron or zinc, antacids, and sucralfate should not be ingested simultaneously with Norfloxacin 400 mg film-coated tablets, as this could reduce Norfloxacin absorption leading to decreased concentrations in the serum and urine. Norfloxacin 400 mg film-coated tablets should be taken either 2 hours before or at least 4 hours after ingesting such

products. This restriction does not apply to H2-receptor antagonist-type antacids. Oral nutritional solutions and dairy products (mild or liquid milk products such as yoghurt) reduce the absorption of Norfloxacin. Norfloxacin should therefore be taken at least 1 hour before or 2 hours after such products.

Drugs known to prolong the QT interval
Norfloxacin400 mg film-coated tablets, 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)

4.6 Pregnancy and lactation

Pregnancy
Norfloxacin should not be used during pregnancy. Norfloxacin and related substances have been shown to cause damage to the articular cartilage in growing animals. The occurrence of such adverse effects in humans cannot be excluded.
Norfloxacin passes in the umbilical cord blood and amniotic fluid.

Lactation
When a 200-mg dose of Norfloxacin was administered to nursing mothers, Norfloxacin was not detected in human milk. However, because the dose studied was low, because other drugs in this class are secreted in human milk, and because damage of articular cartilage in a growing organism was demonstrated, Norfloxacin should only be administered during lactation when strictly indicated.

4.7 Effects on ability to drive and use machines
Even when used correctly, Norfloxacina Sandoz 400 mg film-coated tablets may alter patients' reactivity to the point that their ability to drive or operate machinery is impaired, especially at the start of treatment, on increasing the dose or switching medication, and in conjunction with alcohol.
Fluoroquinolones including Norfloxacin may result in an impairment of the patient's ability to drive or operate machinery due to transient loss of vision (see section 4.8). Patients should be advised to see how they react to Norfloxacin before driving or operating machinery.

4.8 Undesirable effects
Blood and lymphatic system disorders:

The following adverse reactions have been observed in clinical studies or obtained from post-marketing reports: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000), not known (cannot be estimated from the available data)

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Infections and infestations
Uncommon: vaginal candidiasis

Blood and lymphatic system disorders
Common: eosinophilia, leucopenia, neutropenia
Uncommon: thrombocytopenia, reduced hematocrit and prolonged prothrombin time,hemolytic anemia sometimes associated with Glucose-6-phosphate- Dehydrogenase deficiency.

Very rare: agranulocytosis

Immune system disorders
Rare: angioedema, hypersensitivity reaction, vasculitis, anaphylactic reaction, dyspnea, urticaria, petechiae, hemorrhagic bullae, papules with vasculitis.

Metabolism and nutrition disorders
Uncommon: anorexia
Not known: hypoglycaemic coma (see section 4.4)

Psychiatric disorders*
Uncommon: depression, sleep disturbances, nervousness, anxiety
Rare: disorientation, irritability, euphoria, hallucination, psychic disturbances, confusion, psychotic reactions

Nervous system disorders*
Common: headache, dizziness, lightheadedness and drowsiness
Uncommon: paraesthesia, sensory disturbances, dysgeusia, bitter taste, convulsions tremor, polyneuropathy including Guillain-Barré syndrome, myoclonus including exacerbation of myasthenia gravis, tiredness, mood swings, paresthesia, insomnia, depression, anxiety, nervousness, irritability, hallucinations, polyneuropathy including Guillain-Barré syndrome, (epilepsy-like) convulsions, possible exacerbation of myasthenia gravis (see section 4.4).

Eye disorders*
Uncommon: visual disturbances, increased lacrimation
Not known: transient loss of vision

Ear and labyrinth disorders*
Uncommon: tinnitus
Very rare: hearing loss

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Cardiac disorders

Uncommon:	palpitation
Very rare:	QT-prolongation has been reported.
Not known:	ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged (see section 4.4 and 4.9).

Gastrointestinal disorders

Common:	nausea, abdominal pain/cramps, nausea
Uncommon:	diarrhea, heartburn, vomiting, anorexia, pancreatitis, dry mouth, flatulence, dyspepsia, dysphagia, constipation
Rare:	pseudomembranous colitis Uncommon: diarrhea, heartburn, vomiting, anorexia, pancreatitis, dry mouth, flatulence, dyspepsia, dysphagia, constipation
Rare:	pseudomembranous colitis

Hepatobiliary disorders

Common:	elevation of ALAT (SGPT), ASAT (SGOT)
Rare:	jaundice, hepatitis, cholestatic hepatitis

Skin and subcutaneous tissue disorders

Common:	rash
Uncommon:	pruritus, urticarial, severe skin reactions, exfoliative dermatitis, Lyell' syndrome and erythema multiforme (Stevens-Johnson syndrome), photosensitivity, pruritus. Musculoskeletal, connective tissue and bone disorders
Rare:	photosensitivity
Very rare:	rhabdomyolysis
Not known:	leucocytoclastic vasculitis, drug rash with eosinophilia and systemic symptoms (DRESS syndrome).

Musculoskeletal, connective tissue and bone disorders*

Rare:	arthralgia, myalgia, arthritis, tendinitis, tendon rupture

Renal and urinary disorders

Common:	elevated serum creatinine
Uncommon:	elevation of serum urea, crystalluria.
Rare:	interstitial nephritis, renal failure

Investigations

Common:	elevated alkaline phosphatase and LDH
Very rare	elevated creatinine kinase (CK)

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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 (see section 4.4).

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.

4.9 Overdose

At present no experience is available with Norfloxacin overdosing.

In the event of recent acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage, and the patient carefully observed and given symptomatic and supportive treatment.

In recent acute overdosage patients should be advised to drink calcium-containing fluids so that Norfloxacin forms a complex with calcium which undergoes only minimal absorption from the gastro-intestinal tract.

Adequate hydration must be maintained.

Crystalluria was observed in few patients who had been treated with high doses of Norfloxacin. These patients should drink enough liquid to ensure a proper state of hydration.

ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Flouroquinolones
ATC-Code: JO1MAO6/ SO1AE02

5.1 Pharmacodynamic properties

Mode of action:

Norfloxacin has a rapid bactericidal action and inhibits synthesis of bacterial deoxyribonucleic acid (DNA). An enzyme called DNA gyrase plays a key role in this process. Norfloxacin has a broad spectrum of antibacterial activity against gram-positive and gram-negative aerobic bacteria.

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Mechanisms of resistance:

Bacterial resistance against fluoroquinolones is usually based on mechanisms like reduction of quinolone accumulation and/or mutations in the genes that encode for DNA gyrase and topoisomerase IV, the targets of quinolone action.

Bacteria which are resistant to Norfloxacin *in-vitro* are also resistant to the older quinolones.

Several studies have shown that bacteria resistant to Norfloxacin are also generally resistant to pefloxacin, ofloxacin, ciprofloxacin and enoxacin.

There is no cross-resistance to structurally unrelated substances such as penicillins, cephalosporins, tetracyclines, macrolide antibiotics, aminoglycosides and sulfonamides, 2,4-diaminopyrimidine or combinations of these (e.g. cotrimoxazole).

Infections caused by multiply-resistant organisms have been successfully treated with the usual doses of Norfloxacin.

Breakpoints

EUCAST (European Committee on Antimicrobial Susceptibility Testing) recommended clinical MIC breakpoints for Norfloxacin.

Pathogen	**Susceptible**	**Resistant**
Enterobacteriaceae	≤ 0.5 mg/l	> 1 mg/l
Non-species-related breakpoints*	≤ 0.5 mg/l	> 1 mg/l

generally based on serum pharmacokinetics.

Susceptibility

The prevalence of acquired resistance may vary geographically and with 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 ***Gram-negative aerobes*** ***Aeromonas hydrophilia*** *Proteus vulgaris* *Providencia rettgeri* *Salmonella spp* *Shigella spp.*	
Species for which acquired resistance may be a problem ***Gram-positive aerobes*** *Enterococcus faecalis* $ *Stapylococcus aureus* (methicillin-susceptible) *Staphyllococcus saprophyticus*	

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Gram-negative aerobes *Citrobacter freundii* *Enterobacter aerogenes* *Enterobacter cloaca* *Escherichia coli* & *Klebsiella oxytoca* *Klebsiella pneumoniae* *Morganella morganii* *Neisseria gonorrhoeae* *Proteus mirabilis* *Pseudomonas aeruginosa* *Serratia marcescens*	
Inherently resistant organisms ***Gram-positive aerobes*** *Enterococcus faecium* *Staphylococcus aureus* (methicillin-resistant) *Streptococcus agalactiae* ***Gram-negative aerobes*** *Stenotrophomonas maltophilia* ***Anaerobes*** *Clostridium difficile* ***Others*** *Chlamydia trachomatis* *Mycoplasma hominis* *Ureaplasma urealyticum*	

$ The inherent susceptibility of most isolates is within the intermediate range.
& In female patients with uncomplicated cystitis the resistance rate is < 10%, otherwise ≥ 10%.

5.2 Pharmacokinetic properties

Absorption
Norfloxacin is rapidly absorbed after oral administration. In healthy volunteers, at least 30 to 40% of an oral dose is absorbed from the currently available pharmaceutical forms. The presence of food and/or dairy products may decrease absorption.

Distribution
Serum concentrations of 0.84 - 1.64 mg/L were obtained within 1 – 1.5 hours after oral administration of a dose of 400 mg. The time to peak concentration (tmax) ranged from 0.75-2.0 h. The average half-life in serum is three to four hours in healthy volunteers; it is independent of the dosage.
The apparent volume of distribution (Vdβ) is approximately 223 ± 97 I.

Protein binding
Norfloxacin is around 13.8% plasma protein bound at a concentration of 2.5 mgl/l in human serum.

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Elimination

Norfloxacin absorbed from the gastrointestinal tract is eliminated by metabolization and by renal and biliary excretion.

Renal excretion occurs both by glomerular filtration and by tubular secretion, as indicated by the high renal clearance of approximately 236 ± 56 ml/min and the inhibition of probenacid excretion. Total body clearance is 506 ± 211ml/min.

Approximately 25-40% of the dose was recovered in the urine after administration of single and multiple doses of 400 mg PO to renally healthy adult volunteers.

In healthy elderly subjects (65-75 years of age, normal renal function for stated age), Norfloxacin is excreted more slowly in keeping with the physiologically reduced renal function in this age group. Drug absorption appears to be unaffected. The elimination half-life in geriatric patients was 2.7 - 3.5 h after administration of 400 mg/day, and 5.3- 5.4 h after a dose of 400 mg twice daily.

Norfloxacin is recovered intact in the urine and in the form of six active metabolites whose antibacterial efficacy is lower than that of the parent compound. Over 70% of the excreted drug is recovered in non-metabolised form.

Norfloxacin's antibacterial activity is not affected by changes in urinary pH.

Pharmacokinetics in patients with impaired renal function

After a single dose of 400 mg, Norfloxacin is available in patients with a creatinine clearance above 30 ml/min x 1.73 m2 to a similar extent as in healthy volunteers. Renal Norfloxacine excretion is markedly reduced in patients whose creatinine clearance is below 30 ml/min x 1.73 m2. The average Norfloxacin elimination half-life was 4.4, 6.6 and 7.6 h, respectively, in adults with a creatinine clearance of 30-80, 10-29, and below 10 ml/min x 1.73 m2. Peak serum Norfloxacin levels do not appear to be affected in the presence of renal insufficiency.

5.3 Preclinical safety data

As with other quinolones, Norfloxacin caused arthropathy in immature animals. Norfloxacin caused lesions and, in some cases, cartilage erosion in weight baring joints. No arthropathy was seen in monkeys receiving Norfloxacin at doses below 500 mg/kg BW/day (Cmax 15.6 mg/l). Likewise, no such changes were seen in fully-grown animals.

In mice and rats, embryotoxicity was observed, but in rabbits and monkeys, high doses of Norfloxacin resulted in increased embryolethality. Studies on fertility and perinatal and postnatal toxicity disclosed no adverse impact. Norfloxacin can be detected in the amniotic fluid and umbilical cord blood.

Based on the results of animal tests, damage to joint cartilage in the growing body can not entirely be ruled out. Animal studies have revealed no evidence of teratogenicity.

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Tel. : 95250 - 2455801 / 2452714 / 2453525 • Fax : 95250 - 2452074 (0091 - 250 - 2452074) • Email : agog@vsnl.net & agogpharma@rediffmail.com

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Cataractogenic potential

Specific studies investigating the cataractogenic potential of Norfloxacin have not been conducted. As hitherto during therapeutic use no according adverse events have been observed, such studies are not considered necessary at present.

Carcinogenicity

Carcinogenicity studies in rats and mice provided no evidence to suggest carcinogenicity due to Norfloxacin.

Genotoxicity and tumorigenic potential

Norfloxacin may be genotoxic due to its inhibition of topolsomerases in mammalian cells. This effect has a limiting value that is not exceeded in therapeutic use. Long-term studies in rats and mice failed to indicate tumorigenicity.

No photomutagenicity or photocarcinogenicity data are available on Norfloxacin. Comparative data on other fluorquinolones suggest a low photomutagenic/photocarcinogenic potential of Norfloxacin *in vitro* and in animal studies.

6. Pharmaceutical particulars:

6.1 List of Excipients:

Micro Crystalline Cellulose Powder DC Grade 102# 20-24# Mesh.	BP
Micro Crystalline Cellulose Powder	BP
Sodium Starch Glycolate	BP
Colloidal Silicon Dioxide	BP
Talcum	BP
Magnesium Stearate	BP
Polyplasdone XL- (Cross Povidone)	USP
Polacrillin Potassium (KYRON T-314)	USP
Cross Carmellose Sodium	BP

Coating

Colour Instacoat Sol White 010	INH
Iso Propyl Alcohol	BP
Methylene Dichloride	BP

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6.2 Incompatibilities:
None Reported

6.3 Shelf-Life:
36 months from the date of manufacture.

6.4 Special Precautions for Storage:
Store in a cool, dry and dark place. Protect from light.

6.5 Nature and Contents of Container:
Blister Pack of 10×10 Tablets.

6.6 Special precautions for disposal:
None reported.

7. Registrant:

AGOG PHARMA LTD.
Plot No. 33, Sector II,
The Vasai Taluka Industrial
Co-Op. Estate Ltd., Gauraipada,
Vasai (E), Dist. Thane, India.

8. Manufacturer:

AGOG PHARMA LTD.
Plot No. 33, Sector II,
The Vasai Taluka Industrial
Co-Op. Estate Ltd., Gauraipada,
Vasai (E), Dist. Thane,
India.

9. Date of revision of the text: