Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Uroflox 400 mg film-coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Film-coated tablets containing 400 mg norfloxacin.

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

Round, orange film-coated tablet, with an engraved line on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Uroflox 400 mg 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:

- Upper and lower, complicated and uncomplicated, acute and chronic urinary tract infections (including pyelonephritis).
- Urinary infections associated with urological surgery or nephrolithiasis.

Consideration should be given to official local guidance e.g. national recommendations regarding the appropriate use and prescription of antibacterial agents.

4.2 Posology and method of adminstration

The dosage depends on the susceptibility of the pathogens and severity of the disease.

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 cystitis[3]	400 mg twice daily	3 days
Urinary tract infections	400 mg twice daily	7 - 10 days[1]
Chronic relapsing urinary tract infections	400 mg twice daily	Up to 12 weeks[2]

In urinary infections associated with urological surgery or nephrolithiasis the dosage lies between 400 BID – 400 TID. The daily dose and duration of the therapy depends on the severity and relapse rate of the infection.

[1] 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.
[2] If adequate suppression is obtained within the first four weeks of therapy, the dose of Uroflox 400 mg film-coated tablet may be reduced to one tablet once daily.
[3] This condition is considered to be met in women.

The tablets should not be divided.

Dosage for patients with renal insufficiency

Uroflox 400 mg is suitable for treatment of patients with renal insufficiency. In patients with severe impaired renal function, the advantages and disadvantages of the use of Uroflox 400 mg should be carefully weighed up in each individual case. For patients with a creatinine clearance = 30 ml/min x $1.73m^2$ the recommended dosage is 1 Uroflox 400 mg film-coated tablet daily.

At this dosage, fluid and tissue concentrations exceed the MICs 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.

Children and growing adolescents:

Uroflox 400 mg is not recommended for use in children or growing adolescents (see 4.3 Contraindications).

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 day.

4.3 Contraindications

Hypersensitivity to the active substance or to any related quinolone antibacterials, the colouring agent sunset yellow (E110) or to any of the other excipients.

Tendinitis and/or tendon rupture

Norfloxacin is contraindicated in patients with a history of tendinitis and/or tendon rupture related to fluoroquinolone administration (see. 4.4 and 4.8).

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 and efficacy have not yet been sufficiently established for these groups of patients (see sections 4.6 Pregnancy and lactation and 5.3 Preclinical safety data).

4.4 Special warnings and special precautions for use

Photosensitivity

Photosensitivity may occur in patients taking Uroflox 400 mg 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.

Tendinitis and/or tendon rupture

As with other quinolones, tendinitis and/or tendon rupture (particularly affecting the Achilles' tendon) have been observed rarely during and after norfloxacin use. Such reactions have particularly been noted in elderly patients and patients on corticoids. At the first sign of pain or inflammation, norfloxacin therapy should be discontinued immediately and the patient should be given suitable pharmacological treatment.

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 Uroflox 400 mg should be carefully weighed up in each individual case (see section 4.2, Posology and method of administration). 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 a dosage regimen of 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 a proper state of hydration and adequate urinary output.

Pseudomembranous colitis

The occurrence of severe and persistent diarrhea during or after therapy may be an evidence for very rarely observed pseudomembranous colitis. In such cases therapy must be stopped immediately and a suitable therapy (e.g antibiotic with proven clinical efficacy) has to be started. Drugs inhibiting peristalsis are contraindicated.

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity (anaphylactic or anaphylactoid) reactions, some following the first dose, have been reported in patients receiving quinoline therapy. In such cases, therapy with Uroflox 400 mg must be discontinued immediately and appropriate emergency action must be started (e.g. antihistamines, glucocorticosteroids, sympathomimetics and ventilation if necessary).

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 sign 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.

G6PD - (Glucose-6-phosphate-Dehydrogenase) deficiency

In patients with latent or actual G6PD deficiency quinolone class haemolytic reactions are possible.

Sunset yellow (E110) may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Norfloxacin inhibits CYP 1A2 which might lead to interactions with other drugs metabolised by this enzyme.

Nitrofurantoin

In-vitro antagonism has been observed between norfloxacin and nitrofurantoin. Concomitant use of norfloxacin and nitrofurantoin should therefore be avoided.

Probenecid

Probenecid reduces excretion of norfloxacin in the urine but does not influence its serum concentration.

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 theophylline concentration in plasma should thus be monitored and the dosage of theophylline adjusted if necessary.

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.
During treatment with norfloxacin the ingestion of caffeine containing medications (e.g. certain analgesics) should be avoided where possible.

Cyclosporine

Elevated serum concentrations of cyclosporine have been reported with concomitant use of norfloxacin. Therefore, cyclosporine serum concentrations should be monitored and appropriate cyclosporine dosage adjustments made.

Warfarin

Quinolones, including norfloxacin, may enhance the effects of the oral anticoagulant warfarin or its derivatives. If these drugs are administered concomitantly, the prothrombin time or other suitable coagulation tests should be monitored closely.

Fenbufen

According to animal studies, concomitant administration of fluoroquinolones and fenbufen can lead to convulsions. Concomitant use of quinolones and fenbufen should therefore be avoided.

Oral contraceptives

Some antibiotics have been reported to decrease the effect of oral contraceptives.

Miscellaneous preparations (preparations containing iron or antacids, products containing magnesium, aluminium, calcium or zinc)

Multivitamin preparations, preparations containing iron or zinc, antacids, and sucralfate should not be ingested simultaneously with Uroflox 400 mg, as this could reduce norfloxacin absorption leading to decreased concentrations in the serum and urine. Uroflox 400 mg should be taken either 2 hours before or at least 4 hours after ingesting such products. This restriction does not apply to H_2-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.

4.6 Pregnancy and lactation

Pregnant women must not be prescribed norfloxacin since insufficient experience is available on safety of use in this population. On the basis of results from animal studies, damage to articulate cartilage in the immature organism cannot be excluded. Animal studies did not show any evidence of teratogenic effects. Norfloxacin passes into fetus and amniotic fluid.

Since other quinolones are excreted into breastmilk and no data are available for norfloxacin in breastfeeding women, norfloxacin is contraindicated in breastfeeding women or breastfeeding must be discontinued.

4.7 Effects on ability to drive and use machines

Even when used correctly, Uroflox 400 mg 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.

4.8 Undesirable effects

Frequencies: very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100), rare (> 1/10,000, < 1/1000), very rare (< 1/10,000).

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

Immune system disorders
Uncommon: hypersensitivity reactions such as anaphylaxis (see section 4.4 Warnings and precautions), angioedema, urticaria, interstitial nephritis, petechiae, hemorrhagic bullae, papules with vasculitis.

Psychiatric / Nervous system disorders
Common: headache, dizziness, lightheadedness and drowsiness.
Uncommon: tiredness, mood swings, paresthesia, insomnia, sleep disorders, depression, anxiety, nervousness, irritability, euphoria, disorientation, hallucinations, confusion, polyneuropathy including Guillain-Barré syndrome, convulsions psychic disturbances, and psychotic reactions, and possible exacerbation of myasthenia gravis (see section 4.4 Warnings and precautions).

Eye disorders
Uncommon: disturbed vision, increased lacrimation.

Ear and labyrinth disorders
Uncommon: tinnitus.

Cardiac disorders
Uncommon: palpitation
Very rare: QT-prolongation has been reported.

Gastrointestinal disorders
Common: abdominal pain and spasms, nausea.
Uncommon: heartburn and diarrhea, vomiting, anorexia, pancreatitis, hepatitis
Rare: pseudomembranous colitis (see section 4.4 Warnings and precautions).

Hepato-biliary disorders
Uncommon: elevation of serum bilirubin.
Very rare: Cholestatic hepatitis, liver necrosis.

Skin and subcutaneous tissue disorders
Common: rash.
Uncommon: severe skin reactions, exfoliative dermatitis, Lyell's syndrome and erythema multiforme (Stevens-Johnson syndrome), photosensitivity, pruritus.

Musculoskeletal, connective tissue and bone disorders
Uncommon: arthritis, myalgia, arthralgia, tendinitis, tendovaginitis.
Rare: In some cases, inflammation of the Achilles' tendon was observed during treatment with fluoroquinolones including norfloxacin. This may lead to rupture of the Achilles' tendon (see section 4.4, Warnings and Precautions).
Very rare: Rhabdomyolysis.

Unmasking or aggravation of myasthenia gravis (see section 4.4 Warnings and precautions).

Renal and urinary disorders
Uncommon: elevation of serum urea and serum creatinine.

Reproductive system and breast disorders
Uncommon: vaginal candidiasis.

Due to the content of the colouring agent Sunset yellow (E110) allergic reactions may occur.

4.9 Overdose

No experience on norfloxacin overdosage is currently available.

In the case of a recent, acute overdose, the patient should be advised to drink calcium-containing solutions to transform norfloxacin into a calcium complex, which is very poorly absorbed from the gastrointestinal tract. The patient must be carefully monitored and should receive both symptomatic and supportive treatment if necessary. Sufficient fluid intake must be maintained.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones
ATC- Code: J01MA06

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.

The fluorine atom at position 6 increases activity against gram-negative bacteria whereas the piperazine ring at position 7 is responsible for antipseudomonal activity.

At the molecular level, three specific processes are attributed to norfloxacin in Escherichia coli:

1. Inhibition of the ATP-dependent quaternary structural changes (supercoiling reaction) of DNA catalyzed by DNA gyrase.

2. Inhibition of supercoiled DNA relaxation.

3. Promotion of double-stranded DNA breaks.

Breakpoints

The NCCLS (US National Committee on Clinical Laboratory Standards) recommended MIC breakpoints for norfloxacin, separating susceptible (S) from intermediately susceptible organisms (I), and resistant (R) organisms:

$S \leq 4$ mg/l, I = 8 mg/l, $R \geq 16$ mg/l

In the Federal Republic of Germany, DIN 58940 describes the directives for the test methods and the limits for susceptibility/resistance in microbiological studies. The MIC breakpoints for norfloxacin in accordance to DIN 58940 are:

$S \leq 1$ mg/l, I = 2 mg/l, $R \geq 4$ mg/l

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable. 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.

The following table gives norfloxacin's in-vitro spectrum of action, unless otherwise indicated. Values with an asterisk (*) refer to ofloxacin. Unless explicitly stated otherwise, the susceptibility data applicable for Europe are given.

Commonly susceptible species (i.e. resistance < 10% in all EU Member States)	**Percentage resistant [%]**
aerobic Gram-positive micro-organisms	
Staphylococcus saprophyticus in vivo	0
aerobic Gram-negative micro-organisms	
Citrobacter diversus	0
Citrobacter spp.	3.2
Enterobacter cloacae	2.5
Enterobacter spp	9.1
Klebsiella pneumoniae	0 – 8.5
Morganella morganii	0 – 2.4
Proteus mirabilis	0 – 3.6
Proteus vulgaris	3.5

Species for which acquired resistance may be a problem (i.e. resistance > 10% in at least one EU Member State)	**Percentage resistant [%]**
aerobic Gram-positive	
Enterococcus faecalis	52.1 – 80*
Staphylococcus saprophyticus	11.8 – 16
aerobic Gram-negative	
Citrobacter freundii	14.7
Escherichia coli	1.7 – 14.3
Proteus rettgeri	15.4
Pseudomonas aeruginosa	4 – 33.1
Serratia marcescens	22
Serratia spp.	35
Inherently resistant organisms	**Percentage resistant [%]**
aerobic Gram-positive	
Enterococcus faecium	84.6*
Staphylococcus haemolyticus	63.8*
aerobic Gram-negative	
Acinetobacter baumannii	93.3
anaerobic micro-organisms	
all gram-positive anaerobes except some *Clostridium perfringens* strains	
all gram-negative anaerobes	

The note "in vivo" indicates that the stated values refer to the in-vivo bacteriological eradication rate.

Due to its particular structure, norfloxacin may be active against bacteria which are resistant to the older quinolones such as nalidixic acid, oxolinic acid, pipemidic acid, cinoxacin and flumequine. However, these organisms may have higher MICs of norfloxacin than nalidixic acid susceptible strains.

Bacteria which are resistant to norfloxacin in-vitro are also resistant to the older quinolones listed above.

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 otherwise multiresistant organisms have been successfully treated with the usual doses of norfloxacin.

Resistance to norfloxacin due to spontaneous mutations is rare (range: 10^{-9} to 10^{-12} cells). Development of pathogen resistance during therapy with norfloxacin has been observed rarely.

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.

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 l.

Protein binding

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

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 probenecid excretion. Total body clearance is 506 ± 211 ml/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. More than 70% of the excreted drug is recovered in non-metabolized 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 1.73m^2 to a similar extent as in healthy volunteers. Renal norfloxacin excretion is markedly reduced in patients whose creatinine clearance is below 30 ml/min x 1.73m^2. 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 m^2. 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-bearing joints. No arthropathy was seen in monkeys receiving norfloxacin at doses below 500 mg/kg BW/day (C_{max} 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 cannot be entirely ruled out. Animal studies have revealed no evidence of teratogenicity.

Cataractogenic potential

Repeated dose toxicity studies with pigmented animals (dog) should have allowed some estimation of cataractogenic potential. Appropriate experimental studies have not been conducted.

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 topoisomerases 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 fluoroquinolones suggest a low photomutagenic / photocarcinogenic potential of norfloxacin in vitro and in animal studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Povidone
sodium starch glycollate
microcrystalline cellulose
colloidal anhydrous silica
magnesium stearate
purified water

Film-coat:
hypromellose
talc
propylene glycol
colouring agents sunset yellow (E110)
titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Aluminium PVC/PVDC-blister.
Packs with 10, 20, 28, 30, 50, 56 and 100 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Stada Arzneimittel AG,
Stadastrasse 2-18,
D-61118 Bad Vilbel,
Germany.

8 MARKETING AUTHORISATION NUMBER

PA 593/17/1

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