SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Norfloxacin 400 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 400 mg norfloxacin.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablets.
Round, white film-coated tablets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Norfloxacin 400mg tablets is indicated for the treatment of the following bacterial infections caused by pathogens susceptible to norfloxacin: upper and lower complicated and uncomplicated, acute and chronic urinary tract infections, including cystitis, pyelitis, and chronic prostatitis.
Consideration should be given to official local guidance e.g. national recommendations regarding the appropriate use and prescription of antibacterial agents.
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.

4.2 Posology and method of administration

Posology
Dosage in adults
Adults should take 1 film-coated tablet (400 mg norfloxacin) twice daily.

Dosage in elderly patients
Elderly patients should also take 1 film-coated tablet (400 mg norfloxacin) twice daily. Normally, dosage adjustment in this group of patients is not required if there is no significant renal impairment.

**Dosage in patients with impaired renal function**

For all these patients whose creatinine clearance is below 30 ml/min x 1.73 m² and who do not require haemodialysis, the recommended dose is 1 film-coated tablet of *Norfloxacin 400 mg tablets* (400 mg norfloxacin) once daily. At this dosage, concentrations in appropriate body fluids and tissues exceed the MICs for most pathogens responsible for urinary tract infections and sensitive to norfloxacin.

**Paediatric population**

*Norfloxacin 400 mg tablets* is contraindicated in children and growing adolescents (see also 4.3 “Contra-indications”).

**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.

In the case of a single daily dose, this should always be taken at the same time of day.

In women with acute, uncomplicated inflammation of the bladder, a 3 day course of norfloxacin with the recommended dose has frequently proved sufficient.

In the treatment of urinary tract infections, adults will generally need to use *Norfloxacin 400 mg tablets* for 7-10 days.

In case of chronic prostatitis good results were achieved by treatment with the recommended dose for 4 weeks.

The symptoms of urinary tract infection, such as a burning sensation experienced during micturation, pain, and fever, will generally disappear within 1-2 days. However, the treatment course with *Norfloxacin 400 mg tablets* should be continued up to 12 weeks in chronic relapsing urinary tract infections. If adequate suppression is obtained within the first 4 weeks of therapy, the dose may be reduced to 400 mg norfloxacin (1 film-coated tablet) daily.

At present there are no clinical data available for treating patients for more than eight weeks.
4.3 Contraindications

Hypersensitivity to Norfloxacin 400 mg tablets, other chemotherapeutic agents belonging to the quinolone class or any of the excipients.

Norfloxacin should not be used in pregnancy and lactation (see section 4.6).

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

Norfloxacin is contraindicated in prepubertal children and growing adolescents as there are insufficient findings on safety of use in these groups of subjects and, on the basis of results in animal studies, damage to articular cartilage in the immature organism cannot be totally excluded.

4.4 Special warnings and precautions for use

Hypersensitivity reactions
Norfloxacin can cause serious, potentially fatal hypersensitivity reactions (anaphylactic and anaphylactoid reactions), occasionally following the initial dose (see section 4.8). Patients should be advised to discontinue treatment immediately if experiencing such reactions and contact their physician or an emergency physician, who will initiate appropriate emergency measures.

Tendinitis and/or tendon rupture
Norfloxacin should not be used in patients with a present or past injury, inflammation or rupture of the Achilles tendon (see sections 4.3 and 4.8). Tendinitis and/or tendon rupture (particularly the Achilles tendon) may occur with quinolone antibiotics. Such reactions have been observed, particularly in older patients and in those treated concurrently with corticosteroids. On the appearance of tendon pain or signs of inflammation of the Achilles tendon, treatment with norfloxacin must be discontinued immediately and the patient treated accordingly.

Use in patients with epilepsy and other CNS disorders
Norfloxacin 400 mg tablets should only be used if there is an overwhelming clinical need in patients with known epilepsy or disorders which lower the seizure threshold. Convulsions have been reported in rare cases in patients receiving norfloxacin. Norfloxacin may lead to exacerbation and aggravation of the symptoms in patients with known or suspected psychiatric disorders, hallucinations and/or confusion.
In case of convulsive seizures, treatment with norfloxacin should be discontinued

Use in patients with 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.

Use in renal impairment
In patients with severe renal impairment, the risk/benefit ratio of using Norfloxacin 400 mg tablets should be carefully weighed for the individual (see 4.2). The urinary concentration of norfloxacin may be reduced in patients with severely impaired renal function as norfloxacin is predominantly excreted via the kidneys.

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.

Photosensitivity
Photosensitivity reactions have been observed in patients who are exposed to excessive sunlight while receiving some substances of this drugs class. Excessive sunlight and the use of sun beds should be avoided during treatment with norfloxacin. Therapy must be discontinued if photosensitivity occurs.

G6PD-(Glucose-6-phosphate-dehydrogenase) deficiency
In patients with latent or actual G6PD-(Glucose-6-phosphate-dehydrogenase) deficiency quinolone class haemolytic reactions are possible.

Pseudomembranous colitis
The occurrence of severe and persistent diarrhoea 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. vancomycin, 4 x 250 mg by oral route) has to be started. Drugs inhibiting peristalsis are contraindicated.

Cholestatic hepatitis
Cholestatic hepatitis is commonly reported with norfloxacin (see section 4.8)
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.

Vision disorders
If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.
Cardiac disorders
Caution should be taken when using fluoroquinolones, 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.

(See section 4.2 Elderly, section 4.5, section 4.8, section 4.9).

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C.difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C.difficile, and surgical evaluation should be instituted as clinically indicated.

4.5 Interaction with other medicinal products and other forms of interaction

In-vitro antagonism of nitrofurantoin has been demonstrated. Concomitant administration of nitrofurantoin and Norfloxacin 400 mg tablets should therefore be avoided.

Probenecid reduces urinary excretion of norfloxacin, but does not affect its serum concentration.

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

Elevated plasma levels of theophylline have been reported with concomitant theophylline and quinolone use. Isolated cases of theophylline-related side-effects have also been reported in patients on concomitant therapy with norfloxacin and theophylline. Plasma plasma levels of theophylline should therefore be monitored and the dosage adjusted as required.

Co-administration of tizanidine and norfloxacin is not recommended.

The metabolism of caffeine has been shown to be inhibited by quinolones and also by norfloxacin. This can result in delayed elimination and prolonged plasma half-life of caffeine. During treatment with Norfloxacin 400 mg tablets, the ingestion of caffeine-containing medications (e.g. certain analgesics) should therefore be avoided where possible.
Elevated serum levels of ciclosporin have been reported with concomitant use of norfloxacin. Ciclosporin serum concentrations should therefore be monitored and the dosage adjusted as appropriate.

Quinolones, including norfloxacin, may enhance the effects of the oral anticoagulant warfarin or its derivatives. If these medications are given concomitantly, the prothrombin time or other suitable coagulation parameters should be carefully monitored.

Miscellaneous compounds (preparations containing iron/antacids and products containing magnesium, aluminium, calcium or zinc): simultaneous administration of norfloxacin with multivitamin preparations containing calcium, preparations containing iron or zinc, antacids or sucralfate reduces the absorption of norfloxacin, leading to markedly decreased concentrations in serum and urine. Norfloxacin should therefore be taken either 2 hours before or at least 4 hours after such products. The restriction does not apply to H₂-receptor antagonists.

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

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

Oral nutritional solutions and dairy products (milk or 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.

On the basis of animal studies, concomitant administration of quinolones and fenbufen can cause seizures. Co-administration of quinolones and fenbufen should therefore be avoided.

**Drugs known to prolong QT interval**

Norfloxacin, 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) (see section 4.4).

4.6 **Fertility, pregnancy and lactation**
Pregnancy
Pregnant women and breast feeding mothers should not be prescribed 400 mg tablets as there are insufficient findings on safety of use in these groups of subjects and, on the basis of results from animal studies, damage to articular cartilage in the immature organism cannot completely be excluded. Animal studies have not shown any evidence of teratogenic effects. Norfloxacin passes into umbilical blood and amniotic fluid.

Breast-feeding
It is generally known that quinolones pass into mother’s milk. In case of treatment of breast-feeding mothers with norfloxacin, breast feeding must be stopped.

4.7 Effects on ability to drive and use machines
Norfloxacin may alter a patient’s reactivity so that the ability to drive, operate machinery or work without firm support is impaired, especially at the start of treatment, on increasing the dosage or when switching medication and in conjunction with alcohol.

4.8 Undesirable effects

The following convention has been used for the classification of undesirable effects in terms of frequency:- Very common ≥1/10, common ≥1/100 and <1/10, uncommon ≥1/1000 and <1/100, rare ≥1/10,000 and <1/1000, very rare <1/10,000.

Not known (can not be estimated from the available data)

- Blood and the lymphatic system disorders
  uncommon: Leucopenia, neutropenia, eosinophilia, thrombocytopenia, reduced hematocrit, prolongation of prothrombin time.
  rare: Haemolytic anaemia, sometimes associated with Glucose-6-phosphate-dehydrogenase deficiency.

- Immune system disorders
  rare: Anaphylactic/anaphylactoid reactions (see section 4.4).
  not known: Hypersensitivity

- Psychiatric disorders
  rare: Changes of mood, depression, feeling of anxiety, nervousness, irritability, euphoria, disorientation, hallucinations, confusion, psychic disturbances and psychotic reactions.

- Nervous system disorders
  uncommon: Headache, dizziness and drowsiness.
  rare: Paresthesia, insomnia, sleep disturbances, polyneuropathy
including Guillain-Barré syndrome and seizures, and possible exacerbation of myasthenia gravis (see section 4.4).

- **Eye disorders**
  rare: Visual disturbance, increased lacrimation.

- **Ear and labyrinth disorders**
  rare: Tinnitus

- **Cardiac disorders**
  not known: Tachycardia, 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).

- **Vascular disorders**
  rare: Petechiae and haemorrhagic bullae/papules with vasculitis.

- **Gastrointestinal disorders**
  uncommon: Abdominal pain and cramps, heartburn, diarrhoea and nausea.
  rare: Vomiting, loss of appetite, pseudomembranous colitis (see section 4.4), pancreatitis.

- **Hepatobiliary disorders**
  common: Cholestatic hepatitis (see section 4.4), hepatitis.
  uncommon: Elevation of ALT (SGOT), AST (SGPT) and alkaline phosphatase.
  not known: Jaundice

- **Skin and subcutaneous tissue disorders**
  uncommon: Rash
  rare: Skin reactions, exfoliative dermatitis, toxic epidermal necrolysis (Lyell’s syndrome), erythema multiforme (Stevens-Johnson syndrome), photosensitivity (see section 4.4), pruritus and urticaria, angioedema.

- **Musculoskeletal, connective tissue and bone disorders**
  common: Rhabdomyolysis
  rare: Tendinitis, tendosynovitis, (see section 4.4), muscle and/or joint pains, joint inflammation.
  very rare: Rupture of tendons (e.g. Achilles tendon) (see section 4.4).

- **Renal and urinary disorders**
  uncommon: Crystalluria
  rare: Interstitial nephritis

- **Reproductive system and breast disorders**
  rare: Vaginal candidiasis

- **General disorders and administration site conditions**
  rare: Tiredness
Note
Photosensitivity has been observed in patients who, during ongoing therapy with quinolone-like medications, have been extensively exposed to sunlight or sunbeds (phototoxic reactions, photosensitisation with vesiculation, redness, swelling and discoulouration.); (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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose
In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. In the event of acute overdosage, the stomach should be emptied by induced vomiting or by gastric lavage. The patient should be carefully observed and given symptomatic and supportive treatment as required. Adequate hydration must be maintained to prevent crystalluria.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmaco-therapeutic group
Norfloxacin is a bactericidal antibiotic belonging to the group of fluoroquinolones.
ATC Code
J01MA06
Mode of action
Norfloxacin inhibits bacterial deoxyribonucleic acid (DNA) synthesis by inhibition of bacterial topoisomerase II (gyrase) and topoisomerase IV.

Relationship between pharmacokinetics and pharmacodynamics
Efficacy is mainly dependent upon the Cmax (maximum serum concentration):MIC (minimum inhibitory concentration) ratio of the pathogen and the AUC (area under the curve): MIK ratio of the pathogen, respectively.

Mechanism(s) of resistance
Resistance to norfloxacin can derive from the following mechanisms:
- Modified target structures: The main mechanism of resistance against norfloxacin and other fluoroquinolones consists in changes of topoisomerase II and IV as a result of mutation.
Other mechanisms of resistance lead to reduced concentration of fluoroquinolones at the site of action. Therefore liable are a reduced penetration into the bacterial cell due to reduced formation of porins or an increased efflux out of the cell via efflux pumps.

Transferable, plasmid-coded resistance was demonstrated in Escherichia coli and Klebsiella spp.

There is a partial or complete cross-resistance between norfloxacin and other fluoroquinolones.

**Breakpoints**

Testing of norfloxacin is performed by using the usual dilution series. The following minimum inhibitory concentrations were determined for sensitive and resistant micro-organisms:

<table>
<thead>
<tr>
<th>Species</th>
<th>sensitive</th>
<th>resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>≤ 0,5mg/l</td>
<td>&gt; 1mg/l</td>
</tr>
<tr>
<td>Non-species related breakpoints*</td>
<td>≤ 0,5mg/l</td>
<td>&gt; 1mg/l</td>
</tr>
</tbody>
</table>

* based mainly on serum pharmacokinetics

**Prevalence of acquired resistance**

The prevalence of resistance may vary geographically and with time for selected species. Data on the local resistance information are thus desirable, particularly in order to ensure adequate treatment of severe infections. If the local resistance situation puts the efficacy of norfloxacin in doubt, expert therapeutic advice should be sought. Particularly in cases of severe infection or unsuccessful therapy, a microbiological diagnosis with confirmation of the micro-organism and its sensitivity to norfloxacin should be undertaken.

Prevalence of acquired resistance on the basis of data from the past 5 years from national resistance monitoring projects and studies (last revised: December 2007).

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
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</thead>
<tbody>
<tr>
<td><strong>Aerobic Gram-positive micro-organisms</strong></td>
</tr>
<tr>
<td><em>Staphylococcus saprophyticus</em></td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative micro-organisms</strong></td>
</tr>
<tr>
<td><em>Enterobacter aerogenes</em></td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em></td>
</tr>
<tr>
<td><em>Proteus vulgaris</em></td>
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<tr>
<td><em>Salmonella enterica (enteritis salmonella)</em></td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species for which acquired resistance may be a problem</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobic Gram-positive micro-organisms</strong></td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
</tr>
<tr>
<td><em>Staphylococcus aureus (methicillin-sensitive)</em></td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative micro-organisms</strong></td>
</tr>
<tr>
<td><em>Campylobacter jejuni</em></td>
</tr>
<tr>
<td>Citrobacter freundii</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Escherichia coli</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
</tr>
<tr>
<td>Morganella morganii</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
</tr>
</tbody>
</table>

**Inherently resistant organisms**

**Aerobic Gram-positive micro-organisms**

Enterococcus faecium

**Staphylococcus aureus (methicillin-resistant)**

Streptococcus agalactiae

**Aerobic Gram-negative micro-organisms**

Stenotrophomonas maltophilia

**Anaerobic micro-organisms**

Clostridium difficile

**Other micro-organisms**

Chlamydia trachomatis

Mycoplasma hominis

Ureaplasma urealyticum

*At the time of publication of the table, no current data were available. Sensitivity is assumed in the primary literature, standard works and therapy recommendations.*

*Most isolates show natural intermediate susceptibility.*

*Resistance rate in isolates of patients with uncomplicated cystitis is <10%, in others >10%.*

### 5.2 Pharmacokinetic properties

Norfloxacin is rapidly absorbed after oral administration. In healthy volunteers, at least 30-40% of an oral dose is absorbed.

Serum concentrations of 1.5µg/ml are obtained one hour after administration of a dose of 400mg.

The mean serum half-life is three to four hours and independent of the dose. The half-life is doubled in patients with severe renal impairment (creatinine clearance <30ml/min).

Mean concentrations in body fluids and tissues which have been measured 1-4 hours after 2 doses of 400mg norfloxacin were within a range of 1.6-7.3µg/ml.

Norfloxacin is excreted by the kidney and in the bile following partial metabolism.

Renal elimination occurs by glomerular filtration and tubular secretion, as is also apparent from the high renal clearance (approximately 275ml/min).

Norfloxacin is found in urine as the unchanged compound and in the form of 6 active metabolites with slight antibacterial efficacy. The non-metabolised form
constitutes more than 70% of the total elimination. The bactericidal activity of norfloxacin is not influenced by the urinary pH.

Concentrations of 2.5mg/l in human serum leads to binding to plasma proteins of nearly 13.8%.

5.3 Preclinical safety data
As with other quinolones, administration of norfloxacin led to arthropathy in immature animals. No similar pathology has been observed in adult animals. The peak serum levels measured in animal experiments at arthropathic dosages were far higher than the corresponding concentrations in children. However, due to the fact that clinical experience is limited, the use of norfloxacin in children is not recommended.

In mice and rats, embryotoxicity was not observed, but in rabbits and monkeys, high doses of norfloxacin resulted in increased embryolethality.

Norfloxacin (at supra-therapeutic doses) can have genotoxic effects in mammalian cells by inhibition of topoisomerases.

Some fluoroquinolones have weak photomutagenic or phototumorigenic effects in vitro or in animal experiments.

No other significant teratogenic, mutagenic or carcinogenic effects have been observed.

During the years of therapeutic use there have been no grounds for suspecting a potential cataractogenic effect following exposure to norfloxacin. No test that could clarify this damaging quality have been performed with norfloxacin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Povidone, sodium starch glycolate, microcrystalline cellulose, silica colloidal anhydrous, magnesium stearate, purified water, hypromellose, talc, colour titanium dioxide E 171, propylene glycol.

6.2 Incompatibilities
None known

6.3 Shelf life
3 years.
This medication should not be used after the expiry date.

6.4 Special precautions for storage
Store in the original package. Keep blister in the outer carton.
6.5 **Nature and contents of container**
PVC/ PVdC/ A1 blisters

Original pack containing 6 film coated tablets
Original pack containing 10 film coated tablets
Original pack containing 14 film coated tablets
Original pack containing 20 film coated tablets
Original pack containing 50 film coated tablets

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**
Ratiopharm GmbH
Graf-Arco-Str.3
D-89079 Ulm
Germany

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 15773/0002

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION**
02/11/1998

10 **DATE OF REVISION OF THE TEXT**
12/01/2017