Drugs 2004; 64 (19): 2221-2234
0012-6667/04/0019-2221/$34.00/0

Prulifloxacin

Susan J. Keam and *Caroline M. Perry*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ Prulifloxacin, the prodrug of ulifloxacin, is a broad-spectrum oral fluoroquinolone antibacterial agent. After absorption, prulifloxacin is metabolised by esterases to ulifloxacin. The drug has a long elimination half-life, allowing once-daily administration.

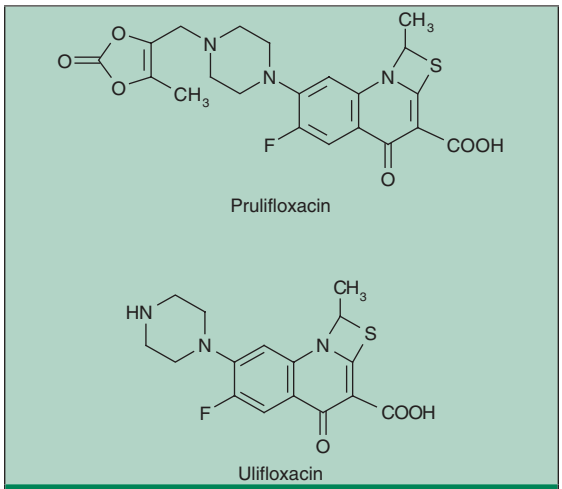
▲ Ulifloxacin is generally more active *in vitro* than other fluoroquinolones against a variety of clinical isolates of Gram-negative bacteria, including community and nosocomial isolates of *Escherichia coli*, *Klebsiella* spp., *Proteus*, *Providencia* and *Morganella* spp., *Moraxella catarrhalis* and *Haemophilus* spp. The activity of ulifloxacin against *Pseudomonas aeruginosa* varies between countries.

▲ Gram-positive organisms, including meticillin- or oxacillin-susceptible *Staphylococcus aureus*, *Enterococcus* spp. and Italian community isolates of *Streptococcus pneumoniae* are susceptible to ulifloxacin. Activity against Spanish strains of *S. pneumoniae* is moderate.

▲ In well designed clinical trials, good clinical and bacteriological efficacy (similar to that of ciprofloxacin, amoxicillin/clavulanic acid or pefloxacin) was seen with prulifloxacin 600mg once daily for 10 days in patients with acute exacerbations of chronic bronchitis or complicated lower urinary tract infections (UTIs), and with single-dose prulifloxacin 600mg in acute, uncomplicated lower UTIs.

▲ Prulifloxacin was generally well tolerated in clinical trials, with a similar tolerability profile to that of ciprofloxacin.

Features and properties of prulifloxacin (Unidrox®)	
Indication	
Acute, uncomplicated lower urinary tract infections (UTIs) [simple cystitis]; complicated lower UTIs; acute exacerbations of chronic bronchitis	
Mechanism of action	
Fluoroquinolone antibacterial agent	Lipophilic prodrug of ulifloxacin; inhibits bacterial DNA gyrase
Dosage and administration	
Recommended dosage	Acute exacerbations of chronic bronchitis: 600 mg/day for a maximum of 10 days; acute, uncomplicated lower UTI: one 600mg tablet; complicated lower UTI: 600 mg/day for a maximum of 10 days
Administration	Oral, once daily
Pharmacokinetic profile of ulifloxacin after oral prulifloxacin 600mg once daily. Mean values (unless stated) after a single dose and at steady state	
Peak plasma concentration	1.6 and 2.0 μg/mL
Median time to peak plasma concentration	1 and 0.75h
Area under the plasma concentration-time curve	7.3 and 7.6 μg • h/mL
Elimination half-life	10.7 and 7.6h
Adverse events	
Most frequent	Gastric disturbances, diarrhoea, nausea, skin rash



Prulifloxacin and its active metabolite

Prulifloxacin (Unidrox®)[1], the lipophilic prodrug of ulifloxacin,[1] is an oral fluoroquinolone antibacterial agent that has a broad spectrum of *in vitro* activity against various Gram-negative and -positive bacteria. After absorption from the gastrointestinal tract, prulifloxacin is rapidly and extensively metabolised to ulifloxacin, the active compound. Like other fluoroquinolones, prulifloxacin prevents bacterial DNA replication, transcription, repair and recombination through inhibition of bacterial DNA gyrase.[2,3] Prulifloxacin has a long elimination half-life, thus allowing once-daily administration, which may contribute to good compliance.[4]

Fluoroquinolones are considered as a first-line therapy in adults with complicated chronic bronchitis[5,6] and as an option in community-acquired pneumonia in immunocompetent adults;[7-9] moreover, ciprofloxacin is the treatment of choice in patients with chronic suppurative bronchitis.[5,6] There is increasing recognition of the role of fluoroquinolones in acute, uncomplicated urinary tract infections (UTIs) in geographic areas where levels of resistance to cotrimoxazole (trimethoprim/sulfamethoxazole) are high.[10-12] In addition, fluoroquinolones may also have a role in the treatment of complicated UTIs.[12,13]

This profile reviews the antibacterial activity, clinical efficacy and tolerability of prulifloxacin, and focuses on recent European trials evaluating the use of once-daily therapy in acute exacerbations of chronic bronchitis (AECB) or complicated lower UTIs, and single-dose prulifloxacin in acute, uncomplicated lower UTIs. The article also reviews data from earlier Japanese studies, where required.

1. Pharmacodynamic Profile

In Vitro Activity

In vitro antimicrobial activity of ulifloxacin was assessed using minimum inhibitory concentrations (MICs) determined by standard broth or agar dilution techniques.[3,14,15] Although data from two earlier Japanese studies that assessed the *in vitro* activity of ulifloxacin are available,[1,16] susceptibility testing reported in this profile is based on published European data obtained between 1998 and 2000,[14,15] supplemented by data from the manufacturer's investigator's brochure[3] and an unpublished study.[17] These studies used methods recommended by the National Committee for Clinical Laboratory Standards (NCCLS).[18]

For reference drugs, results were interpreted using NCCLS breakpoints.[19,20] *In vitro* antibacterial studies were performed using ulifloxacin;[3,14,15] the proposed European susceptibility breakpoints for ulifloxacin are ≤1, 2 and ≥4 mg/L for susceptible, intermediate and resistant strains.[3] MIC_{50} and MIC_{90} refer to the minimum concentrations of the antibacterial agent required to inhibit growth of 50% or 90% of microorganisms.

Representative studies from Italy[14] and Spain[15] indicated that, like other fluoroquinolones (including ciprofloxacin, levofloxacin, ofloxacin, trovafloxacin and moxifloxacin), ulifloxacin has *in vitro* activity against a variety of clinical isolates of Gram-negative or -positive bacteria commonly associated with chronic lower respiratory tract infections or lower UTIs (table I). Ulifloxacin showed limited activity against *Chlamydia pneumoniae*, an

1 The use of trade names is for product identification purposes only and does not imply endorsement.

atypical respiratory tract pathogen (MIC_{90} 4 mg/L), and against anaerobic bacteria.[3]

Gram-Negative Bacteria

- The *in vitro* activity of ulifloxacin was generally greater than that of ciprofloxacin and other fluoroquinolones, including moxifloxacin, against Italian nosocomial and community isolates[14] and Spanish clinical isolates[15] of Gram-negative bacteria, such as *Escherichia coli*, *Klebsiella* spp., *Proteus*, *Providencia* and *Morganella* spp., *Pseudomonas aeruginosa*, *Moraxella catarrhalis* and *Haemophilus* spp.
- Ulifloxacin was highly active against many Enterobacteriaceae, including Italian community or nosocomial isolates[14] and Spanish clinical isolates of *E. coli*[15] (with activity against some nalidixic acid-resistant isolates[15]) and *Klebsiella* spp. (MIC_{90} ≤0.015–4.0 mg/L). The MIC_{90} value for ulifloxacin against Italian nosocomial isolates of *Klebsiella* spp. was 2 mg/L versus 8 mg/L for ciprofloxacin.[14] Ulifloxacin demonstrated strong activity against Italian nosocomial and community isolates[14] and Spanish clinical isolates[15] of *Proteus* (nalidixic acid-susceptible isolates only in Spain[15]), *Providencia* and *Morganella* spp. (MIC_{90} ≤0.015–0.5 mg/L).
- Common respiratory tract pathogens are highly susceptible to ulifloxacin, including Italian community[14] and Spanish clinical[15] isolates of *Haemophilus* spp. (with activity against *H. influenzae*[15]), *M. catarrhalis*,[14,15] β-lactamase-producing strains of *H. influenzae* or *M. catarrhalis*[3] and Spanish clinical isolates[15] of nalidixic acid-susceptible or -resistant *K. pneumoniae* (MIC_{90} values of ≤0.12–0.25 mg/L).
- Ulifloxacin showed good activity against Spanish clinical isolates of ciprofloxacin-susceptible *P. aeruginosa* (MIC_{90} 1.0 mg/L)[15] and gentamicin-resistant *P. aeruginosa* (MIC_{90} 0.2 mg/L).[3] However, like other fluoroquinolones, ulifloxacin had negligible activity against Italian nosocomial and community isolates of *P. aeruginosa*,[14] Spanish clinical isolates of ciprofloxacin-resistant *P. aeruginosa*[15] and nalidixic acid-resistant *P. aeruginosa*[3] (MIC_{90} values of >4 mg/L).
- Emerging bacterial resistance in Gram-negative pathogens after repeated exposure to ulifloxacin was generally similar to that seen with other fluoroquinolones, including ciprofloxacin.[3] After seven passages at subinhibitory concentrations of either agent in *in vitro* studies, the MIC of ulifloxacin against *E. coli* was unchanged and that of ciprofloxacin was increased 2-fold. Against *P. aeruginosa*, the MIC of ulifloxacin increased 4-fold, and that of ciprofloxacin increased 16-fold.[3]

Gram-Positive Bacteria

- The *in vitro* activity of ulifloxacin against Italian nosocomial and community isolates[14] or Spanish clinical isolates[15] of Gram-positive bacteria, including *Streptococcus* spp., *Staphylococcus aureus*, *Enterococcus* spp. and coagulase-negative staphylococci was generally similar to or greater than that of ciprofloxacin, but less than that of moxifloxacin.[14]
- Susceptibility of *Streptococcus* spp. (including *S. pneumoniae*) to ulifloxacin varied between countries.[14,15] Italian community isolates of *S. pneumoniae* and Italian community or Spanish clinical isolates of *S. pyogenes*[15] were susceptible to ulifloxacin (MIC_{90} 1.0 mg/L).[14] However, ulifloxacin (and ciprofloxacin) had moderate or low activity against penicillin-susceptible, -intermediate or -resistant Spanish clinical strains of *S. pneumoniae* (ulifloxacin or ciprofloxacin MIC_{90} values of 2–4 mg/L), unlike moxifloxacin (all MIC_{90} 0.12 mg/L).[15]
- Italian nosocomial and community isolates[14] and Spanish isolates[15] of oxacillin- or meticillin-susceptible *S. aureus* were highly susceptible to ulifloxacin (MIC_{90} values of ≤0.5 mg/L). The MIC_{90} values for ulifloxacin against Italian community isolates of *Enterococcus* spp.,[14] and Italian nosocomial[14] or Spanish[15] isolates of the common urinary tract pathogen *E. faecalis* were 1, 2 and 4 mg/L, respectively.
- Like ciprofloxacin, ulifloxacin had negligible activity against Italian nosocomial isolates[14] and Spanish clinical isolates[15] of oxacillin- or meticillin-resistant *S. aureus* (MIC_{90} >4 mg/L). However, ulifloxacin was active against fluoroquinolone-resistant *S. aureus*.[3,17] Ulifloxacin and ciproflox-

Table I. *In vitro* activity of ulifloxacin and ciprofloxacin against Gram-negative and -positive bacteria (MIC and MBC values [mg/L]).[a] Data from studies conducted in Italy[14] and Spain[15] comparing ulifloxacin with other fluoroquinolones against clinical isolates obtained between 1998 and 2000

Species (no. of isolates)	Ulifloxacin			Ciprofloxacin		
	MIC_{50}	MIC_{90}	MBC_{90}	MIC_{50}	MIC_{90}	MBC_{90}
Gram-negative bacteria						
Escherichia coli						
Italian nosocomial (41)	≤0.015	4.0	16	≤0.015	16.0	32
Italian community (37)	≤0.015	0.12	0.5	≤0.015	0.5	1
Spanish [nalidixic acid-resistant] (26)	≤0.015 [0.12]	≤0.015 [1]	NT	≤0.015 [0.25]	≤0.015 [1]	NT
Haemophilus spp., Italian community (24)	≤0.015	≤0.015	0.03	≤0.015	≤0.015	0.03
H. influenzae, Spanish (20)	≤0.015	≤0.015	NT	≤0.015	0.03	NT
Klebsiella spp.						
Italian nosocomial (33)	≤0.015	2	4	0.03	8	16
Italian community (15)	≤0.015	0.12	0.12	0.03	0.25	0.25
K. pneumoniae, Spanish [nalidixic acid-resistant] (23)	0.03 [0.25]	0.12 [0.25]	NT	0.03 [0.25]	0.25 [1]	NT
Moraxella catarrhalis						
Italian community (16)	≤0.015	0.03	0.03	≤0.015	≤0.015	0.03
Spanish (8)	0.03	0.06	NT	0.12	0.12	NT
Proteus, Providencia, Morganella spp.						
Italian nosocomial (44)	≤0.015	0.5	0.5	0.03	2	2
Italian community (23)	≤0.015	0.5	1	0.03	1	4
P. mirabilis, Spanish [nalidixic acid-resistant] (22)	≤0.015 [1]	≤0.015 [>4]	NT	0.03 [>4]	0.03 [>4]	NT
Pseudomonas aeruginosa						
Italian nosocomial (45)	2	64	64	8	128	128
Italian community (16)	1	32	128	2	64	128
Spanish [ciprofloxacin-sensitive] (75)	0.25	1	NT	0.5	1	NT
Gram-positive bacteria						
Enterococcus spp., Italian community (19)[b]	0.5	1	4	0.5	1	2
E. faecalis, Italian nosocomial (26)	0.5	2	16	1	2	8
E. faecalis, Spanish [vancomycin-resistant] (21)	2 [4]	4 [>4]	NT	1 [>4]	1 [>4]	NT
Staphylococcus aureus						
Italian nosocomial, oxacillin-susceptible (30)	0.25	0.25	0.5	0.25	0.5	1
Italian community, oxacillin-susceptible (26)	0.25	0.25	0.5	0.25	0.5	0.5
Spanish [meticillin-resistant] (20)	0.5 [>4]	0.5 [>4]	NT	0.5 [>4]	0.5 [>4]	NT
Streptococcus pneumoniae						
Italian community (36)	0.5	1	2	0.5	1	2
Spanish penicillin-susceptible, -intermediate or -resistant (58)	1–2	2–4	NT	1–2	2–4	NT
S. pyogenes						
Italian community (21)	0.25	1	2	0.25	1	4
Spanish (17)	0.25	0.25	NT	0.5	1	NT

a The proposed European susceptibility breakpoints for ulifloxacin were ≤1, 2 and ≥4 mg/L for susceptible, intermediate and resistant strains of bacterial species.[3] For ciprofloxacin, year 2000 NCCLS susceptibility breakpoints were ≤1, 2 and ≥4 mg/L.[19]

b Sixteen strains of *E. faecalis*, 2 strains of *E. faecium* and 1 strain of *E. durans*.

MBC_{90} = minimum concentration required to kill 90% of isolates; **MIC_x** = minimum concentration required to inhibit *x*% of isolates; **NCCLS** = National Committee for Clinical Laboratory Standards; **NT** = not tested.

acin had negligible activity against Italian nosocomial isolates of oxacillin-susceptible (MIC_{90} 8 vs 16 mg/L) or -resistant (MIC_{90} 64 vs 64 mg/L) coagulase-negative staphylococci.[14] Spanish iso-

lates of vancomycin-resistant *E. faecalis* were resistant to both ulifloxacin and ciprofloxacin, with MIC_{90} values >4 mg/L.[15]

- The extent of the emergence of resistant strains of *S. aureus* and meticillin-resistant *S. aureus* after *in vitro* exposure to subinhibitory concentrations of ulifloxacin (MIC values increased 32- and 4-fold after seven passages) was generally similar to that seen with other fluoroquinolones, including ciprofloxacin (MIC values increased 16- and 2-fold).[3] Resistance data for other Gram-positive bacteria were not assessed.

Bactericidal Activity

- The bactericidal activity of ulifloxacin (assessed by the minimum bactericidal concentration [MBC] required to kill 90% of organisms) against a variety of susceptible Italian nosocomial and/or community isolates, including *Klebsiella* spp., *Proteus*, *Providencia* and *Morganella* spp., *Haemophilus* spp. and *M. catarrhalis* was equal to or within two times the MIC_{90} values, whereas the MBC_{90} values for nosocomial and community isolates of *E. coli* spp. were 4-fold higher than the MIC_{90} (table I).[14]
- Ulifloxacin MBC_{90} values against susceptible Italian nosocomial and/or community bacterial isolates of oxacillin-susceptible *S. aureus*, *S. pneumoniae* and *S. pyogenes* were 2-fold higher than the MIC_{90} values; those against susceptible isolates of *Enterococcus* spp. were 4- and 8-fold higher than the MIC_{90} values (table I).[14]

In Vivo Activity

- Comparative data suggest that prulifloxacin has similar or greater activity than ciprofloxacin or ofloxacin against Gram-negative (including *E. coli*, *K. pneumoniae* and *P. aeruginosa*) or -positive organisms (including *S. aureus* and *S. pneumoniae*) in mouse models of systemic[1,21] or respiratory tract[1] infection or UTI.[1,22]
- In a representative mouse model of systemic infection,[21] prulifloxacin showed protective effects similar to those of ciprofloxacin or ofloxacin against *S. aureus* (corresponding doses required to protect 50% [ED_{50}] of mice were 4.52, 10.99 and 5.97 mg/kg, respectively), *E. coli* (ED_{50} 0.36, 0.45 and 0.55 mg/kg, respectively) and *K. pneumoniae* (ED_{50} 0.56, 1.18 and 1.1 mg/kg, respectively). ED_{50} values with prulifloxacin were approximately 2- to 5-fold lower than those of ciprofloxacin or ofloxacin against *S. pneumoniae* (ED_{50} 23.08, 112.31 and 48.81 mg/kg, respectively) or *P. aeruginosa* (ED_{50} 24.94, 46.5 and 93.0 mg/kg, respectively).[21]
- In a mouse model of respiratory infection, the prulifloxacin ED_{50} value was up to 2-fold lower than that of ciprofloxacin or ofloxacin against *K. pneumoniae* (ED_{50} 0.98, 2.24 and 1.18 mg/kg, respectively).[1] Prulifloxacin showed similar or greater therapeutic efficacy to that of ciprofloxacin[22] and superior efficacy to ofloxacin or levofloxacin (measured by reductions in bacterial counts) against *E. coli* or *P. aeruginosa* in mouse models of UTI.[1,22]

Cardiac Risk, Proconvulsant and Phototoxicity Potential

- Results of *in vitro*[23] and *in vivo*[23,24] studies suggest that the QT interval is unlikely to be prolonged during prulifloxacin therapy. Ulifloxacin, like ciprofloxacin, had little effect *in vitro* on the human ether-a-go-go-related gene (HERG) K^+ channel in stable transfected human embryonic kidney cells; unlike moxifloxacin (50% inhibitory concentration of 74.7 μmol/L), neither agent achieved a 50% inhibition of HERG current amplitude at 0.1 Hz with concentrations of up to 335 μmol/L (maximum blockades of 12.3% for ulifloxacin and 47.6% for ciprofloxacin).[23]
- Oral administration of prulifloxacin 150 mg/kg once daily for 5 days in conscious dogs had no effect on the PR, QT or corrected QT (Fridericia's formula) intervals.[23] Like levofloxacin, a continuous intravenous infusion of ulifloxacin 4 mg/kg/min in anaesthetised rabbits did not prolong the QT interval or induce cardiac arrhythmias.[24]
- As with other fluoroquinolones, such as ciprofloxacin, oral prulifloxacin did not induce convulsions in mice.[25] However, oral coadministration of prulifloxacin or ciprofloxacin with fenbufen, an NSAID, induced convulsions and death in mice.[25]

The convulsant effect of prulifloxacin in this model was similar to that of ciprofloxacin when either drug was coadministered orally with theophylline.[25]

- The phototoxic potential of prulifloxacin appears to be low, and similar to that of ciprofloxacin.[3] In a randomised, single-blind, crossover study with a 15-day washout period, no phototoxic reaction was observed in seven of ten healthy Caucasian males in each treatment group. Volunteers were exposed to ultraviolet A irradiation before and after 8 days' administration of oral prulifloxacin 600mg once daily or ciprofloxacin 500mg twice daily. One prulifloxacin recipient developed mild phototoxicity, while the two other phototoxic reactions were considered doubtful or probable. Ciprofloxacin caused doubtful phototoxicity in two of ten subjects and probable phototoxicity in one subject.[3]

2. Pharmacokinetic Profile

The pharmacokinetics of oral prulifloxacin after single- or multiple-dose administration have been evaluated, including in several dose-ranging studies, in young or elderly, healthy Japanese or Caucasian volunteers and in patients with renal impairment.[3,26-32] Data from European studies[26,27,31,32] are supplemented by those from Japanese studies[28-30] and the manufacturer's investigator's brochure,[3] where required.

Because oral prulifloxacin is a prodrug and is rapidly and extensively metabolised to ulifloxacin (after administration, there are no detectable concentrations of prulifloxacin found in plasma), the pharmacokinetics of oral prulifloxacin have been determined by evaluating plasma and urine concentrations of ulifloxacin.[3,26-31] Discussion in this section focuses predominantly on data for single-dose or once-daily prulifloxacin 600mg. Values are means, unless otherwise stated.

Absorption and Distribution

- After administration of a single oral dose of prulifloxacin 600mg in young healthy Caucasian volunteers, the peak plasma concentration (C_{max}) of ulifloxacin (1.6 μg/mL) was achieved in a median time to C_{max} (t_{max}) of 1 hour.[26] The area under the plasma concentration-time curve from zero to infinity (AUC_∞) was 7.3 μg • h/mL, and AUC_∞ values showed linearity over a dose range of 300–600mg ($p < 0.05$).[26]

- At steady state, the ulifloxacin C_{max} was 2 μg/mL after administration of prulifloxacin 600mg once daily for 12 days, with corresponding t_{max} (median) and AUC_{ss} values of 0.75 hours and 7.6 μg • h/mL.[3,31] Prulifloxacin absorption (evidenced by an approximately 30% reduction in ulifloxacin C_{max} and AUC values) is reduced when the drug is taken with milk.[30]

- Ulifloxacin is ≈45% bound to serum proteins *in vivo*.[3] It is extensively distributed throughout tissues, with an apparent volume of distribution of 1231L after a single dose of prulifloxacin 600mg, and shows good penetration into many body tissues.[3]

- After administration of a single dose of prulifloxacin 600mg to patients with lung cancer who were undergoing pneumonectomy/lobectomy, concentrations of ulifloxacin in lung tissue were 1.24 and 0.48 μg/g at 2 and 24 hours after administration. Ulifloxacin lung/plasma concentration ratios increased with time, and concentrations of the active compound in lung tissue at 2, 12 and 24 hours after administration were approximately 2-, 3- and 5-fold greater than the corresponding plasma concentrations.[3]

- Like other fluoroquinolones, ulifloxacin actively penetrates into phagocytic cells *in vitro*.[3,33-35] The mean maximum intracellular : extracellular concentration ratio of ulifloxacin in human polymorphonuclear leukocytes was 12.3 after exposure to an *in vitro* concentration of 20 μg/mL.[35] In mouse peritoneal macrophages, the ratios were 1.23–8.93 after exposure to *in vitro* concentrations of ulifloxacin 0.25–4 μg/mL over 24 hours.[34] Ulifloxacin showed intracellular bactericidal activity against phagocytosed *P. aeruginosa*,[35] *K. pneumoniae*[33,34] and *S. aureus*[3] and appeared to potentiate *in vitro* macrophage activity.[33,34]

- Penetration of ulifloxacin into the CNS is poor, with low or no concentrations of ulifloxacin detected in cerebrospinal fluid after single- or multiple-dose administration of prulifloxacin.[3]

Metabolism and Elimination

- After absorption from the gastrointestinal tract, prulifloxacin undergoes extensive first-pass metabolism (hydrolysis by esterases, mainly paraoxonase[36]) to form ulifloxacin, the active metabolite.[3] Unchanged ulifloxacin is predominantly eliminated by renal excretion.[26] Urinary concentrations of ulifloxacin were >3 μg/mL at 48 hours after a single dose of prulifloxacin 600mg.[26]
- The elimination of ulifloxacin is not dose-dependent.[26] The elimination half-life ($t_{1/2}$) of ulifloxacin after single-dose prulifloxacin 300–600mg ranged from 10.6 to 12.1 hours.[26] Ulifloxacin urinary excretion (Ae) values were significantly correlated with AUC_∞ values ($r^2 = 0.86$; $p < 0.001$), rather than with the administered dose of prulifloxacin 300–600mg.[26] Renal clearance (CL_R) of ulifloxacin was ≈170 mL/min, irrespective of the dose.[26]
- At 48 hours after administration, 17–23% of a single dose of prulifloxacin 300–600mg was excreted as ulifloxacin in the urine and 17–29% in the faeces.[26,37] Approximately 7% of an administered dose of prulifloxacin is excreted as inactive metabolites.[3]
- Steady-state ulifloxacin $t_{1/2}$ and CL_R values were 7.6 hours and 193 mL/min when prulifloxacin 600mg was administered once daily for 12 days;[31] these values are similar to those reported in the published single-dose study.[26] Eighteen percent of the administered dose of prulifloxacin that was excreted in the urine as ulifloxacin at steady state.[3,31]

Special Patient Populations

- The pharmacokinetics of ulifloxacin have been assessed in healthy, elderly Caucasian volunteers (aged >65 years) who received single-dose prulifloxacin 600mg.[3] Although the C_{max} value (1.73 μg/mL) in these subjects was similar to those reported in studies in healthy individuals aged 18–40 years, t_{max} (1.3 hours), AUC_∞ (11.44 μg • h/mL) and $t_{1/2}$ (13.4 hours) values were increased by 23–57%. However, CL_R (168 mL/min) and the proportion of the administered prulifloxacin dose that was excreted in the urine as ulifloxacin (21%) were similar to values seen in studies in younger volunteers.[3]
- In patients with mild (creatinine clearance [CL_{CR}] 41–60 mL/min or 2.5–3.6 L/h) or moderate (CL_{CR} 20–40 mL/min or 1.2–2.4 L/h) renal impairment, changes in ulifloxacin pharmacokinetic parameters after administration of prulifloxacin (prolonged t_{max}, increased AUC and $t_{1/2}$, decreased Ae and CL_R) were correlated to the severity of renal impairment.[3,32] Consequently, dosage adjustment in patients with any degree of renal impairment is recommended.[3]

Drug Interactions

- Systemic exposure to theophylline is increased when it is coadministered with fluoroquinolones, including prulifloxacin.[27] Theophylline AUC and $t_{1/2}$ values increased by ≈15% and apparent oral clearance decreased by ≈15% when prulifloxacin 600mg was administered once daily for 8 days with coadministration of theophylline 6 mg/kg on days 1 and 7 in young, healthy volunteers.[27] Other pharmacokinetic parameters were unchanged.[27]
- Although this effect is unlikely to be clinically important, and is definitely lower than that reported for ciprofloxacin (increase of serum theophylline concentrations up to 308%),[38] monitoring of serum theophylline concentrations is recommended if the drugs are administered together.[27]
- The absorption of oral prulifloxacin was reduced when cimetidine, aluminium-, magnesium- or calcium-containing antacids or iron supplements were coadministered, or administered up to 3 hours before or up to 2 hours after prulifloxacin.[29]
- Concurrent administration of probenecid and oral prulifloxacin increased systemic exposure to ulifloxacin by 46%, prolonged the ulifloxacin $t_{1/2}$ by 60% and reduced the apparent total clearance and urinary excretion of ulifloxacin by 30% and 57%, suggesting that renal excretion of ulifloxacin is via active tubular secretion as well as glomerular filtration.[28]

3. Therapeutic Efficacy

The clinical efficacy of prulifloxacin has been evaluated in randomised, comparative, multicentre studies conducted in France, Italy and Switzerland (some of which were double-blind,[3,4,39-41]) in patients with AECB[3,4,41] or acute, uncomplicated[3,39,42] or complicated lower UTIs.[3,37,40,43] Study drugs were administered orally as a single dose in acute, uncomplicated lower UTI (prulifloxacin 600mg,[3,39,42] ciprofloxacin 500mg[3,39] or pefloxacin 800mg[42]) or once (prulifloxacin 600mg[3,4,40,41,43]) or twice (ciprofloxacin 500mg[3,4,40] or amoxicillin/clavulanic acid 1g [amoxicillin 882.55mg and clavulanic acid 125.28mg; Augmentin®][3,41,43]) daily for 10 days in complicated lower UTIs[3,37,40,43] or AECB.[3,4,41]

From a statistical viewpoint, prulifloxacin was considered to be statistically noninferior to the reference drug in these studies if the lower limit of the one-tailed 95% confidence interval (CI) for the difference between efficacy rates was ≤15%,[3,4,40-43] except for the double-blind ciprofloxacin-controlled study in patients with acute uncomplicated UTIs,[39] which was designed as a superiority trial.

Fully published studies in AECB[4] and acute lower UTIs[42] are supplemented by the manufacturer's data on file from two studies in these indications;[3,39,41] studies in complicated lower UTIs are only available as an abstract[37] and as data on file.[3,40,43]

Acute Exacerbations of Chronic Bronchitis

The comparative efficacy of once-daily prulifloxacin 600mg,[3,4,41] twice-daily ciprofloxacin 500mg[4] or twice-daily amoxicillin/clavulanic acid 1g[3,41] administered for 10 days in the treatment of AECB has been evaluated in two double-blind, double-dummy studies in 235[4] and 214[3,41] adult patients (mean age ≈65 years). In both studies,[3,4,41] eligible patients had chronic bronchitis (cough with productive sputum for ≥3 consecutive months for >2 consecutive years) and at least two of the following symptoms/signs: increased cough and/or dyspnoea; increased sputum volume; increased sputum purulence. Exclusion criteria included x-ray evidence of pneumonia, concurrent infections, recent antibacterial therapy, or significant hepatic or renal impairment.[3,4,41]

Patients were assessed four times during the study: at baseline; on day 5–7 of treatment; on day 10–12 (0–48 hours after ceasing treatment); at the follow-up visit 2 weeks after completing treatment.[3,4,41] The clinical outcome (primary endpoint) was assessed at the end-of-treatment (EOT) visit. Therapeutic success was defined as clinical cure (resolution of all baseline symptoms) or improvement (decrease in intensity of all baseline symptoms).[4,41]

Microbiological assessment of sputum samples was carried out before and after treatment and at the follow-up visit, if required. Microbiological success at EOT was defined as eradication (the pathogen observed at baseline was not present) or presumed eradication (sputum sample not available because patient was clinically cured at endpoint). Evidence of persistence (original pathogen present at EOT) or superinfection (new pathogen at EOT, with or without the original pathogen) was also noted.[3,4,41] Efficacy analyses were modified intent-to-treat (MITT; 224 randomised patients with baseline and final evaluations) and per-protocol (PP; n = 222) in the published study[4] and intent-to-treat (ITT) or PP (both n = 212) in the unpublished study.[3,41] MITT analyses are discussed in preference to PP data, when applicable.

- In the published study, 103 causative bacterial strains were identified at baseline in 50 prulifloxacin and 44 ciprofloxacin recipients (42.5% of 221 microbiologically evaluable patients).[4] The most common organisms were *H. influenzae* (30.6%), *S. pneumoniae* (18.9%), *K. pneumoniae* (11.7%) and *P. aeruginosa* (8.1%). Bacteriological response according to the infecting pathogen is shown in figure 1.[4]

- Therapeutic success rates at EOT (MITT analysis) were similar with prulifloxacin or ciprofloxacin, being 84.7% (95% CI 78.0, 91.4) versus 85.0% (95% CI 78.4, 91.5).[4] Similar proportions of prulifloxacin and ciprofloxacin recipients in the MITT

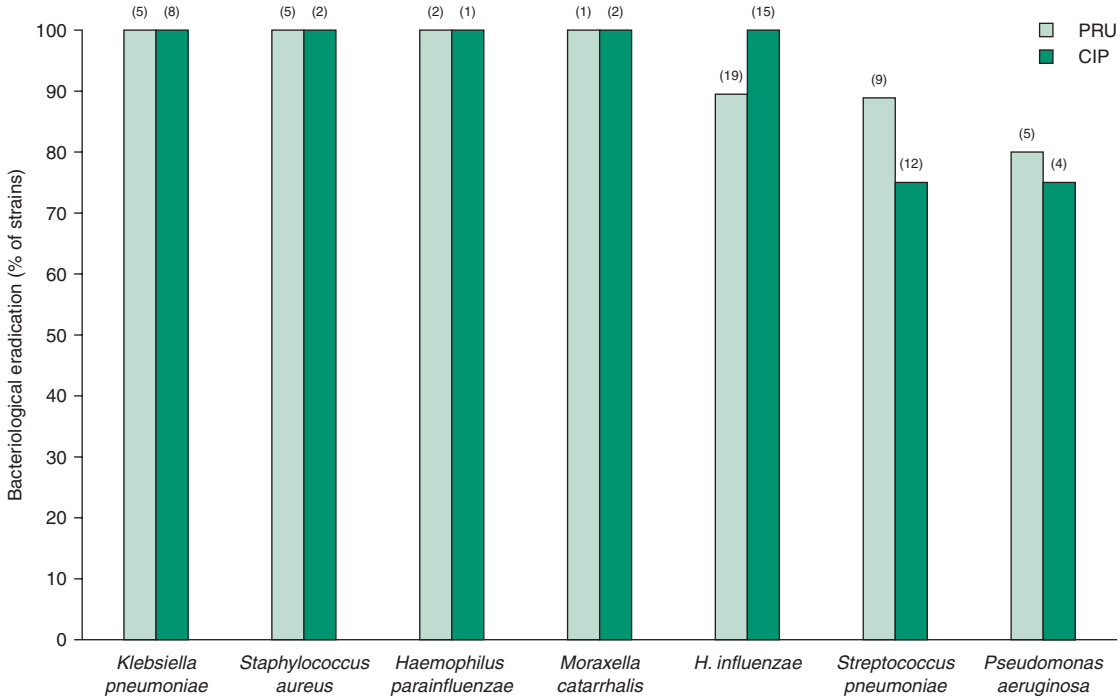


Fig. 1. Bacterial eradication rates with prulifloxacin (PRU) or ciprofloxacin (CIP). Percentage actual and presumed bacteriological eradication by pathogen at the end-of-treatment visit (0–48 hours after the end of treatment). Patients with acute exacerbations of chronic bronchitis received oral PRU 600mg once daily (n = 117) or CIP 500mg twice daily (n = 118) for 10 days in a randomised, double-blind, double-dummy trial.[4] Number of strains of each pathogen at baseline are shown in parentheses.

population achieved a clinical cure (15.3% vs 11.5%) or improvement (69.4% vs 73.5%). Prulifloxacin was statistically noninferior to ciprofloxacin.[4]

- Microbiological success at EOT with prulifloxacin was generally similar to that with ciprofloxacin (figure 1).[4] Bacteriological assessment at EOT showed superinfection (*P. aeruginosa* [two isolates], *K. oxytoca* and *S. aureus*) in four patients (two in each treatment group) who were clinically cured and with no evidence of the initial causative pathogen.[4]
- At the follow-up assessment, 2 of 91 prulifloxacin and 1 of 93 ciprofloxacin recipients had clinical evidence of relapse (exacerbation of chronic bronchitis) compared with EOT.[4] Microbiological assessment in patients whose condition had deteriorated at follow-up showed persistence in two instances (*Pseudomonas* spp. in one prulifloxacin recipient; *S. pneumoniae* in one ciprofloxacin recipient).[4]
- In the unpublished study,[3,41] 155 bacterial strains were identified at baseline; the most common pathogens were *E. coli* (16.7%), coagulase-negative *Staphylococcus* spp. (14.8%) and *K. pneumoniae* (12.9%).
- Therapeutic success rates at EOT were similar with prulifloxacin or amoxicillin/clavulanic acid, being 92.5% (95% CI 87.4, 97.5) versus 93.4% (95% CI 88.6, 98.1).[3,41] Statistical analyses demonstrated therapeutic equivalence of prulifloxacin and amoxicillin/clavulanic acid (lower limit of the one-tailed 95% CI −6.7%).[41] Two weeks after completing treatment, therapeutic success rates were 94.2% with prulifloxacin and 98.0% with amoxicillin/clavulanic acid.[3,41]
- Microbiological success at EOT was documented in 94.9% (95% CI 90.0, 99.8) of prulifloxacin and 93.1% (95% CI 87.3, 99.0) of amoxicillin/clavulanic acid recipients.[3,41]

Acute, Uncomplicated Lower Urinary Tract Infections

The efficacy of single-dose prulifloxacin 600mg was compared with that of single-dose pefloxacin 800mg[42] or ciprofloxacin 500mg[3,39] in a published, nonblind study (n = 239)[42] and an unpublished double-blind study (n = 251)[3,39] in women (mean age ≈40 years) with acute uncomplicated UTIs (simple cystitis). In the pefloxacin-controlled study,[42] women outpatients with acute, uncomplicated lower UTIs, evidenced by bacteriuria (uropathogenic strains $\geq 10^5$ cfu/mL susceptible or moderately susceptible to the study drugs), pyuria and <10 days of dysuria and/or urgency, frequency or suprapubic pain were eligible for inclusion. At the time of study entry, the mean duration of the current UTI was 2–3 days.[42]

Exclusion criteria included recurrent cystitis, pyelonephritis, complicated UTIs, fever, pregnancy or lactation, history of altered cerebral conditions, use of antimicrobial agents, xanthines or fenbufen in the previous 2 weeks, and renal or hepatic impairment. Patients were assessed at baseline, after 5–7 days (follow-up 1 [FU1]) and at 4 weeks (FU2) after ceasing treatment.[39,42]

The primary efficacy endpoint in both studies was the microbiological eradication of infecting pathogens, based on the results of urine cultures at the follow-up assessments.[3,39,42] Successful bacteriological eradication was no bacteria or $<10^3$ cfu/mL bacteria; treatment failure ($\geq 10^3$ cfu/mL at any time) was classed as persistence (the original pathogen was present at FU1), relapse (the original pathogen was not detected at first follow-up but was present at FU2) or superinfection/reinfection (a new pathogen present at concentrations $\geq 10^5$ cfu/mL). Clinical success (secondary endpoint) was clinical cure or improvement (all baseline symptoms resolved or decreased in intensity).[3,39,42] Efficacy analyses are ITT, unless otherwise stated.[3,39,42]

- In the pefloxacin-controlled study,[42] 231 causative bacterial strains were isolated at baseline in the ITT population (n = 231). The most common organisms were *E. coli* (71.4%), *P. mirabilis* (10.8%) and *K. pneumoniae* (7.8%). Bacteriological response according to the infecting pathogen is shown in figure 2.[42]

- Successful bacteriological eradication at FU1 and FU2 was seen in similar proportions of prulifloxacin and pefloxacin recipients (mean differences at these timepoints of 5.2% and 1.8%; one-tailed 95% CI 0.5, 10.0 and −1.1, 4.6), and no relapses, reinfections or superinfections were seen at FU2 in patients achieving microbiological success.[42] Persistence was observed in three prulifloxacin and nine pefloxacin recipients at FU1.[42]

- Likewise, clinical success rates with prulifloxacin or pefloxacin at FU1 (92.2% vs 84.3%) and FU2 (97.4% vs 96.5%) were similar, and prulifloxacin was statistically noninferior to pefloxacin (mean differences 7.9% and 0.9%; one-tailed 95% CI 1.0, 14.8 and −2.8, 4.6).[42] Clinical failure (which occurred in 7.8% and 15.7% of prulifloxacin or pefloxacin recipients) was due to the persistence and/or lack of improvement of one or more baseline symptoms.[42]

- At FU2, three patients who had achieved clinical success at FU1 had recurrence of symptoms without

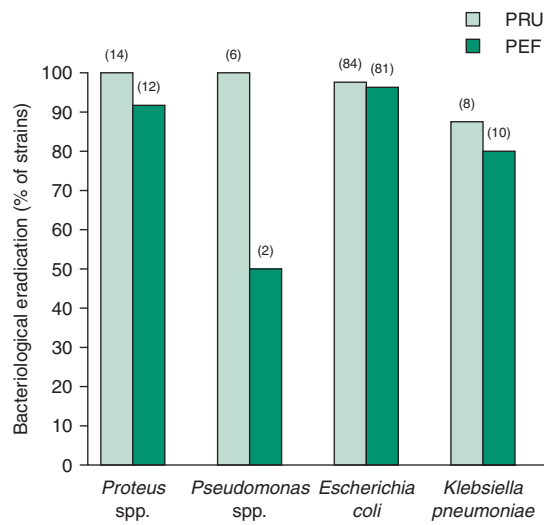


Fig. 2. Bacterial eradication rates with prulifloxacin (PRU) or pefloxacin (PEF). Percentage bacteriological eradication by pathogen at the first follow-up visit (5–7 days after treatment cessation). Patients with acute, uncomplicated lower urinary tract infections (simple cystitis) received a single oral dose of PRU 600mg (n = 116) or PEF 800mg (n = 115) in a randomised, nonblind study.[42] Number of strains of each pathogen at baseline are shown in parentheses.

evidence of urinary pathogens (two prulifloxacin and one pefloxacin recipient).[42]

- In the unpublished study,[3,39] 246 causative bacterial strains were isolated at baseline in 241 patients, predominantly *E. coli* (60.2%), *P. mirabilis* (7.7%) and coagulase-negative *Staphylococcus* spp. (6.1%).
- Similar proportions of prulifloxacin or ciprofloxacin recipients achieved bacteriological eradication at 5–7 days after treatment (97.2% vs 97.2%; both 95% CI 94.0, 100.0; PP analysis).[3,39] ITT analysis showed similar results (95.0% vs 93.3% at 5–7 days; 95% CI 89.1, 100.0 and 89.9, 97.8). At 30 days after treatment, bacteriological eradication was maintained in almost all patients (95.2% vs 95.4%; 95% CI 91.2, 99.3 and 91.4, 99.3; PP analysis).
- Clinical success rates at 5–7 days (98.1% vs 98.2%; 95% CI 95.5, 100.0 and 95.6, 100) and at 30 days (97.1% vs 96.3%; 95% CI 94.0, 100.0 and 92.7 and 99.9) after prulifloxacin or ciprofloxacin therapy were also similar (PP analyses).[3,39]

Complicated Lower Urinary Tract Infections

The efficacy of prulifloxacin 600mg once daily for 10 days has been compared with that of twice-daily ciprofloxacin 500mg (n = 257)[3,40] or amoxicillin/clavulanic acid 1g (n = 225)[3,43] in patients aged 18–89 years with complicated UTIs in two European trials,[3,37,40,43] one of which was double-blind.[3,40]

Complicated lower urinary tract infection was defined as the presence of an indwelling catheter, intermittent catheterisation, a residual urine after voiding of ≥50mL, prostatic hypertrophy, obstructive uropathy, vesicourethral reflux or other urological abnormalities characterised by any combination of dysuria, urgency, frequency, suprapubic pain or fever.[3,40,43]

Patients were enrolled when the UTI was confirmed by culture of a midstream urinary specimen exhibiting ≥10^5 cfu/mL of bacterial strains susceptible or intermediate to the treatment drugs. The presence of pyuria (white blood cell count ≥10/mm^3 or ≥5/high-powered field) was also required. Exclusion

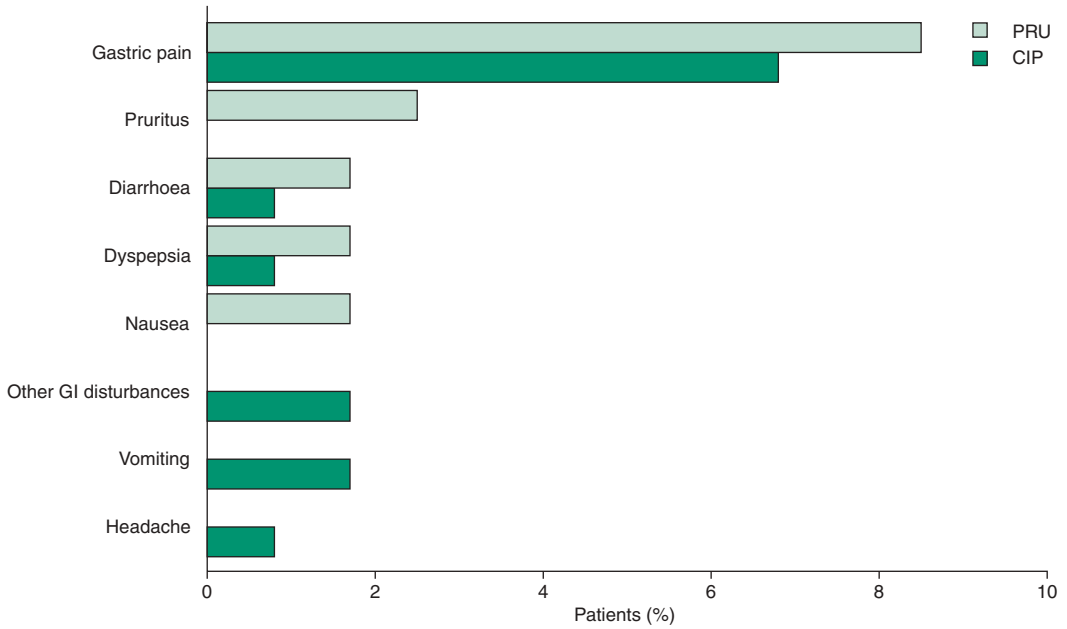


Fig. 4. Tolerability of prulifloxacin (PRU). Drug-related, treatment-emergent adverse events reported in patients with acute exacerbations of chronic bronchitis who received oral PRU 600mg once daily (n = 117) or ciprofloxacin (CIP) 500mg twice daily (n = 118) for 10 days in a multicentre, randomised, double-blind, double-dummy trial.[4] **GI** = gastrointestinal.

criteria included prostatitis, vesiculitis and epididymitis, pregnancy or lactation, history of altered cerebral conditions, use of antimicrobial agents in the previous 3 weeks, concomitant treatment with xanthines or fenbufen, and renal or hepatic impairment.[3,40,43]

In both studies, patients were evaluated at four interviews (baseline; days 5–7 during treatment; days 5–7 after treatment [FU1]; 4 weeks post-treatment [FU2]).[3,40,43]

The primary efficacy endpoint was microbiological eradication of infecting pathogens, based on the results of urine cultures at follow-up assessments.[3,40,43] Successful bacteriological eradication was no bacteria or $<10^3$ cfu/mL bacteria. Treatment failure ($\geq 10^3$ cfu/mL at any time) was classed as persistence (the original pathogen was present at FU1), relapse (the original pathogen was not detected at first follow-up but was present at FU2) or superinfection/reinfection (a new pathogen present at concentrations $\geq 10^3$ cfu/mL). Clinical success (secondary endpoint) was clinical cure or improvement (all baseline symptoms resolved or decreased in intensity).[3,40,43]

- In these two studies, the predominant bacterial strains at baseline were *E. coli* (62.8% in the double-blind comparison with ciprofloxacin and 47.9% in the comparison with amoxicillin/clavulanic acid), *P. mirabilis* (7.0% and 15.5%) and *K. pneumoniae* (4.1% and 7.3%).[3,40,43]

- According to the PP analysis (n = 193), successful bacteriological eradication at FU1 was achieved in 90.4% (95% CI 84.5, 96.4) of prulifloxacin and 80.8% (95% CI 73.1, 88.6) of ciprofloxacin recipients in the double-blind comparison.[3,40] ITT analysis (n = 206) using the Z test showed that prulifloxacin was significantly more effective than ciprofloxacin in achieving successful bacteriological eradication at FU1 (Z = 2.63; p = 0.008) [figure 3].[3,40]

- Clinical success was seen in the majority of prulifloxacin or ciprofloxacin recipients (94.9% vs 92.0%; 95% CI 90.4, 99.2 and 86.7, 97.3; PP analysis).[3,40]

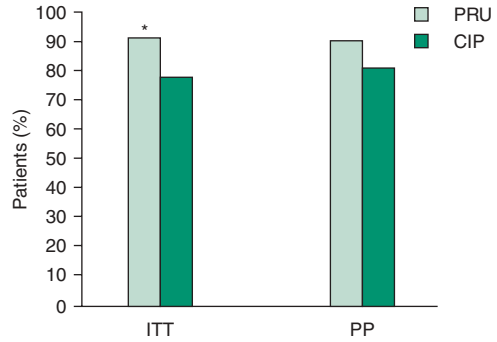


Fig. 3. Comparative efficacy of prulifloxacin (PRU) and ciprofloxacin (CIP). The proportion of patients with complicated lower urinary tract infections receiving PRU 600mg once daily (n = 127) or CIP 500mg twice daily (n = 130) for 10 days at the first follow-up visit (5–7 days post-treatment) who achieved successful bacteriological eradication (n = 206 evaluable patients; intent-to-treat [ITT] analysis; n = 193; per-protocol [PP] analysis) in a randomised, double-blind study.[3,40] * p = 0.008 vs CIP.

- At FU2, similar proportions of prulifloxacin and ciprofloxacin recipients had evidence of bacteriological success (75.3% vs 72.2%).[3,40]

- In the nonblind study, PP analysis indicated that successful bacteriological eradication at FU1 occurred in similar proportions of prulifloxacin and amoxicillin/clavulanic acid recipients (n = 204; 93.1% vs 95.1%; 95% CI 88.2, 98.0 and 90.9, 99.3), an outcome that was unchanged at FU2 (93.5% vs 93.7%).[3,43] Statistical analysis demonstrated therapeutic equivalence (lower limit of the one-tailed 95% CI −7.4%). The clinical success rates with either treatment were similar (96.1% vs 97.1%; 95% CI 92.3, 99.8 and 93.8, 100.0).[3,43]

4. Tolerability

- Prulifloxacin was generally well tolerated in the clinical trials discussed in section 3. There were no significant differences in the type, severity and incidence of treatment-related adverse events in multiple- or single-dose comparisons of prulifloxacin with ciprofloxacin,[3,4,39,40] pefloxacin,[42] or amoxicillin/clavulanic acid.[3,41,43]

- Similar proportions of prulifloxacin and ciprofloxacin recipients with AECB reported drug-related, treatment-emergent adverse events during 10 days of therapy (15.4% vs 12.7%; n = 235)

[figure 4].[4] The most frequently reported treatment-related adverse event in either group was mild or moderate gastric pain (8.5% vs 6.8%).[4] One patient in each treatment group withdrew prematurely because of treatment-related adverse events.[4] Prulifloxacin was not associated with clinically significant changes from baseline in vital signs, haematology or biochemistry.[4]

- Single-dose prulifloxacin was well tolerated.[42] In the comparison with pefloxacin, only one possible treatment-related adverse event (gastric pain with prulifloxacin) was reported.[42]
- The incidence of treatment-related adverse effects with prulifloxacin in a combined analysis of phase II/III European and Japanese data was 4.6% (207 adverse events reported by 180 of 3845 patients).[3,37] Treatment-related adverse events with ciprofloxacin (449 patients), ofloxacin (449 patients), amoxicillin/clavulanic acid (220 patients) or single-dose pefloxacin (118 patients), the comparator drugs, occurred in 7.6%, 6.4%, 16.8% and 0% of patients, respectively.[3]
- The most frequently reported adverse events were gastric disturbances (62 of 207 events), diarrhoea (26), nausea (24) and skin rash (13).[3]

5. Dosage and Administration

In Italy, approval is being sought for the use of oral prulifloxacin 600mg as a single dose in the treatment of acute uncomplicated lower UTIs, and as a once-daily 600mg dosage for a maximum of 10 days in the treatment of complicated lower UTIs or AECB.[3]

6. Prulifloxacin: Current Status

Prulifloxacin is an oral fluoroquinolone that has activity against a wide range of pathogens, including those frequently associated with respiratory tract infections and UTIs. It was approved in Japan in 2002 for use in a variety of infections.[44] Once prulifloxacin is approved in Italy, approval in other European countries will be sought.[45]

References

1. Ozaki M, Matsuda M, Tomii Y, et al. *In vivo* evaluation of NM441, a new thiazeto-quinoline derivative. Antimicrob Agents Chemother 1991 Dec; 35 (12): 2496-9
2. Hooper D. Mode of action of fluoroquinolones. Drugs 1999; 58 Suppl. 2: 6-10
3. Angelini ACRAF S.p.A. Investigator's brochure: Unidrox® prulifloxacin 600mg tablets. Rome: ACRAF S.p.A., 2004 Apr 20. (Data on file)
4. Grassi C, Salvatori E, Rosignoli MT, et al. Randomized, double-blind study of prulifloxacin versus ciprofloxacin in patients with acute exacerbation of chronic bronchitis. Respiration 2002; 69 (3): 217-22
5. Grossman RF. Guidelines for the treatment of acute exacerbation of chronic bronchitis. Chest 1997; 112 Suppl.: 310S-3S
6. Balter MS, La Forge J, Low DE, et al. Canadian guidelines for the management of acute exacerbation of chronic bronchitis: Canadian Thoracic Society and the Canadian Infectious Disease Society. Can Respir J 2003; 10 Suppl. B: 3B-32B
7. American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia: diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001 Jun; 163 (7): 1730-54
8. Heffelfinger JD, Dowell SF, Jorgensen JH, et al. Management of community-acquired pneumonia in the era of pneumococcal resistance: a report from the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group. Arch Intern Med 2000 May 22; 160 (10): 1399-408
9. Mandell LA, Bartlett JG, Dowell SF, et al. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis 2003; 37: 1405-33
10. Warren JW, Abrutyn E, Hebel JR, et al. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women: Infectious Diseases Society of America (IDSA). Clin Infect Dis 1999 Oct; 29 (4): 745-58
11. Hooten TM. Fluoroquinolones and resistance in the treatment of uncomplicated urinary tract infection. Int J Antimicrob Agents 2003; 22 Suppl.: S65-72
12. Naber KG, Bergman B, Bishop MC, et al. EAU guidelines for the management of urinary and male genital tract infections: Urinary Tract Infection (UTI) Working Group of the Health Care Office (HCO) of the European Association of Urology (EAU). Eur Urol 2001; 40: 576-88
13. Melekos MD, Naber KG. Complicated urinary tract infections. Int J Antimicrob Agents 2000; 15: 247-56
14. Montanari MP, Mingoia M, Varaldo PE. *In vitro* antibacterial activities of AF 3013, the active metabolite of prulifloxacin, against nosocomial and community Italian isolates. Antimicrob Agents Chemother 2001 Dec; 45 (12): 3616-22
15. Prats G, Roig C, Miro E, et al. *In vitro* activity of the active metabolite of prulifloxacin (AF 3013) compared with six other fluoroquinolones [published erratum appears in Eur J Clin Microbiol Infect Dis 2004; 23: 422]. Eur J Clin Microbiol Infect Dis 2002 Apr; 21 (4): 328-34
16. Yoshida T, Mitsuhashi S. Antibacterial activity of NM394, the active form of prodrug NM441, a new quinolone. Antimicrob Agents Chemother 1993 Apr; 37 (4): 793-800
17. Tomii Y, Sumumura N, Kitamura J. Comparison of NM394 with other drugs in antibacterial activity against quinolone-resistant bacteria. Kyoto: Nippon Shinyaku Co. Ltd, 1996 Nov 11. (Data on file)

18. National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A5. 5th ed. Wayne (PA): National Committee for Clinical Laboratory Standards, 2000

19. National Committee for Clinical Laboratory Standards. MIC testing supplemental tables. M100-S10 (M7). Wayne (PA): National Committee for Clinical Laboratory Standards, 2000

20. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial susceptibility testing: fourteenth informational supplement M100-S14. Wayne (PA): National Committee for Clinical Laboratory Standards, 2004

21. Nishino T, Tomii Y, Shibata K, et al. *In vitro* and *in vivo* antibacterial activity of NM441 [in Japanese]. Jpn J Chemother 1996; 44 Suppl. 1: 56-69

22. Tomii Y, Ozaki M, Matsuda M, et al. Therapeutic effect of the quinolone prodrug prulifloxacin against experimental urinary tract infections in mice. Arzneimittelforschung 1996; 46 (II): 1169-73

23. Lacroix P, Crumb WJ, Durando L, et al. Prulifloxacin: *in vitro* (HERG current) and *in vivo* (conscious dog) assessment of cardiac risk. Eur J Pharmacol 2003 Sep 5; 477 (1): 69-72

24. Akita M, Shibazaki Y, Izumi M, et al. Comparative assessment of prulifloxacin, sparfloxacin, gatifloxacin and levofloxacin in the rabbit model of proarrhythmia. J Toxicol Sci 2004 Feb; 29 (1): 63-71

25. Ukai Y, Yamazaki A, Kurosaka C, et al. Convulsant effects of NM441, a prodrug type antibacterial agent of the quinolone class [in Japanese]. Jpn J Chemother 1996; 44 Suppl. 1: 102-12

26. Picollo R, Brion N, Gualano V, et al. Pharmacokinetics and tolerability of prulifloxacin after single oral administration. Arzneim.-Forsch./Drug Res 2003; 53 (3): 201-5

27. Fattore C, Cipolla G, Gatti G, et al. Pharmacokinetic interactions between theophylline and prulifloxacin in healthy volunteers. Clin Drug Invest 1998 Nov; 16 (5): 387-92

28. Totsuka K, Kikuchi K, Shimizu K. Pharmacokinetics in concomitant administration with probenecid and clinical study of NM441 (in Japanese). Jpn J Chemother 1996; 44 Suppl. 1: 279-88

29. Shiba K, Yoshida M, Sakai O, et al. Pharmacokinetics and clinical studies on NM441 [in Japanese]. Jpn J Chemother 1996; 44 Suppl. 1: 263-78

30. Saito A, Tarao F. Influence of milk on absorption of NM441, a prodrug type of quinolone antibiotic [in Japanese]. Jpn J Chemother 1996; 44 Suppl. 1: 221-8

31. Mignot A, Millerioux L, Berland C, et al. A repeat dose study of NM441 in healthy volunteers. Rome: Angelini Ricerche S.p.A., 2001 May 7. (Data on file)

32. Villa G, Olivieri L, Picollo R, et al. Safety, tolerability and pharmacokinetic evaluation of prulifloxacin (AF3012) 600mg single dose in patients with mild or moderate renal impairment. Rome: Angelini Ricerche S.p.A., 1998 Aug 28. (Data on file)

33. Tullio V, Cuffini AM, Bonino A, et al. Influence of a new fluoroquinolone, AF3013 (the active metabolite of prulifloxacin), on macrophage functions against *Klebsiella pneumoniae*: an *in vitro* comparison with pefloxacin. J Antimicrob Chemother 2000 Aug; 46 (2): 241-7

34. Tullio V, Cuffini AM, Bonino A, et al. Cellular uptake and intraphagocytic activity of the new fluoroquinolone AF 3013 against *Klebsiella pneumoniae*. Drugs Exptl Clin Res 1999; XXV (1): 1-11

35. Ozaki M, Komori K, Matsuda M, et al. Uptake and intracellular activity of NM394, a new quinolone, in human polymorphonuclear leukocytes. Antimicrob Agents Chemother 1996 Mar; 40 (3): 739-42

36. Tougou K, Nakamura A, Watanabe S, et al. Paraoxonase has a major role in the hydrolysis of prulifloxacin (NM441), a prodrug of a new antibacterial agent. Drug Metab Dispos 1998 Apr; 26 (4): 355-9

37. Gialdroni Grassi G. Prulifloxacin [abstract]. Attualità e Controversie in Terapia Antinfettiva; 2000 Mar 22-25; Verona

38. Davis R, Markham A, Balfour JA. Ciprofloxacin: an updated review of its pharmacology, therapeutic efficacy and tolerability. Drugs 1996 Jun; 51 (6): 1019-74

39. Zagni R, Orticelli G, Rosignoli MT, et al. Double-blind, controlled study of prulifloxacin in comparison with ciprofloxacin in the treatment of acute uncomplicated lower urinary tract infections. Rome: Angelini Ricerche S.p.A., 1998 Jun 27. (Data on file)

40. Carmignani G, Caranti S, Rosignoli MT, et al. Double blind ciprofloxacin controlled study of prulifloxacin in the treatment of complicated lower urinary tract infections. Rome: Angelini Ricerche S.p.A., 1998 Jul 15. (Data on file)

41. Grassi C, Salvatori E, Martini A, et al. Evaluation of efficacy and tolerability of prulifloxacin versus amoxi-clavulanic acid in the treatment of acute exacerbations of chronic bronchitis. Rome: Angelini Ricerche S.p.A., 1998 May 27. (Data on file)

42. Cervigni M, Orticelli G, Bologna M, et al. Single-dose prulifloxacin versus single-dose pefloxacin in the treatment of acute uncomplicated urinary tract infection in women. Urogynaecol Int 2003; 17 (2): 69-77

43. Defidio L, Olivieri L, Rosignoli MT, et al. Efficacy and tolerability of prulifloxacin versus amoxi-clavulanic acid in the treatment of complicated urinary tract infections. Rome: Angelini Ricerche S.p.A., 1998 May 27. (Data on file)

44. Prulifloxacin approved in Japan. Scrip 2002 Oct 16; (2790): 22

45. Prulifloxacin. NAD-441A, NM 441, Quisnon. Drugs R D 2002; 3 (6): 426-30

Correspondence: *Susan J. Keam,* Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 1311, New Zealand.
E-mail: demail@adis.co.nz