ADIS DRUG EVALUATION

Drugs 1998 Sep; 56 (3): 487-515
0012-6667/98/0009-0487/$29.00/0

Levofloxacin

Its Use in Infections of the Respiratory Tract, Skin, Soft Tissues and Urinary Tract

Heather D. Langtry and *Harriet M. Lamb*

Adis International Limited, Auckland, New Zealand

Various sections of the manuscript reviewed by:

P.H. Edelstein, Department of Pathology and Laboratory Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania, USA; ***T.M. File,*** Akron Infectious Disease, Inc., Akron, Ohio, USA; ***R.N. Grüneberg,*** Department of Clinical Microbiology, University College London Hospitals, London, England; ***K.P. Klugman,*** School of Pathology, South African Institute for Medical Research, University of the Witwatersrand, Johannesburg, South Africa; ***T.J. Marrie,*** Department of Microbiology & Immunology, Division of Infectious Diseases, Faculty of Medicine, Halifax, Nova Scotia, Canada; ***S.R. Norrby,*** Department of Infectious Diseases, University of Lund, Lund University Hospital, Lund, Sweden; ***K.A. Rodvold,*** Department of Pharmacy Practice, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois, USA.

Data Selection

Sources: Medical literature published in any language since 1966 on levofloxacin, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase search terms were 'levofloxacin' and 'infections'. Medline and EMBASE search terms were 'levofloxacin', 'infections', 'therapeutic use', 'pharmacokinetics' and 'pharmacology'. Searches were last updated 3 Aug 1998.

Selection: Studies in patients with bacterial infections who received levofloxacin. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: levofloxacin, community-acquired pneumonia, chronic bronchitis, acute maxillary sinusitis, skin and soft tissue infections, urinary tract infections, pyelonephritis, pharmacokinetics, pharmacodynamics, therapeutic use.

Contents

Summary

Abstract

Levofloxacin, the optically pure levorotatory isomer of ofloxacin, is a fluoroquinolone antibacterial agent. Like other fluoroquinolones, it acts on bacterial topoisomerase and has activity against a broad range of Gram-positive and Gram-negative organisms. Levofloxacin also appears to have improved activity against *Streptococcus pneumoniae* compared with ciprofloxacin or ofloxacin. Levofloxacin distributes well and achieves high levels in excess of plasma concentrations in many tissues (e.g. lung, skin, prostate). High oral bioavailability allows switching from intravenous to oral therapy without dosage adjustment.

In patients with mild to severe community-acquired pneumonia receiving treatment for 7 to 14 days, oral levofloxacin was similar in efficacy to amoxicillin/clavulanic acid, and intravenous and/or oral levofloxacin was superior to intravenous ceftriaxone and/or oral cefuroxime axetil. With levofloxacin use, clinical success (clinical cure or improvement) rates were 87 to 96% and bacteriological eradication rates were 87 to 100%. In the 5- to 10-day treatment of acute exacerbations of chronic bronchitis, oral levofloxacin was similar in efficacy to oral cefuroxime axetil or cefaclor. Levofloxacin resulted in clinical success in 78 to 94.6% of patients and bacteriological eradication in 77 to 97%. Oral levofloxacin was also similar in efficacy to amoxicillin/clavulanic acid or oral clarithromycin in patients with acute maxillary sinusitis treated for 7 to 14 days.

Equivalence between 7- to 10-day therapy with oral levofloxacin and ciprofloxacin was seen in patients with uncomplicated skin and soft tissue infections. Clinical success was seen in 97.8 and 96.1% of levofloxacin recipients and bacteriological eradication in 97.5 and 93.2%. Complicated urinary tract infections, including pyelonephritis, responded similarly well to oral levofloxacin or ciprofloxacin for 10 days or lomefloxacin for 14 days. Clinical success and bacteriological eradication rates with levofloxacin occurred in 92 to 93.3% and 93.6 to 94.7% of patients.

Conclusions: Levofloxacin can be administered in a once-daily regimen as an alternative to other fluoroquinolones in the treatment of infections of the urinary tract, skin and soft tissues. Its more interesting use is as an alternative to established treatments of respiratory tract infections. *S. pneumoniae* appears to

be more susceptible to levofloxacin than to ciprofloxacin or ofloxacin. Other newer fluoroquinolone agents that also have enhanced *in vitro* antipneumococcal activity may not share the well established tolerability profile of levofloxacin, which also appears to improve on that of some older fluoroquinolones.

Pharmacology

Levofloxacin has a broad range of activity against Gram-positive and Gram-negative, atypical and intracellular bacteria and is moderately active against anaerobes.

Methicillin- or oxacillin-susceptible staphylococci (including *Staphylococcus aureus*, *S. saprophyticus* and *S. epidermidis*) are also susceptible to levofloxacin. Levofloxacin is similar in activity against methicillin- or oxacillin-susceptible *S. epidermidis* to ofloxacin or ciprofloxacin, but less active against these strains than sparfloxacin or trovafloxacin. However, staphylococci that were resistant to methicillin or oxacillin were also resistant to levofloxacin, ciprofloxacin, ofloxacin and sparfloxacin.

Streptococcus pneumoniae that were susceptible, intermediately susceptible or resistant to penicillin and *S. pyogenes* were all susceptible to levofloxacin. When evaluated on the basis of a 2-dilution difference between agents, the inhibitory activity of levofloxacin against *S. pneumoniae* appeared to be similar to that of ofloxacin, ciprofloxacin and sparfloxacin, but less than that of trovafloxacin. However, at optimum bactericidal concentrations, levofloxacin is more active against *S. pneumoniae* than ofloxacin, ciprofloxacin or sparfloxacin. Further, *S. pneumoniae* strains had minimum inhibitory concentrations below National Committee for Clinical Laboratory Standards recommended susceptibility breakpoints for levofloxacin but not for ofloxacin.

Most enterococci and Enterobacteriaceae were susceptible to levofloxacin, including *Enterococcus faecalis*, *Citrobacter freundii*, *C. diversus*, *Enterobacter aerogenes*, *E. cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca*, *Morganella morganii*, *Proteus mirabilis* and *P. vulgaris*. However, *Providencia stuartii* and *P. rettgeri* were resistant or had intermediate susceptibility; most *Serratia* spp. were only intermediately susceptible. *E.coli* and *K. pneumoniae* with cephalosporin resistance were also resistant to levofloxacin. Resistance of these organisms to other fluoroquinolones tested was also evident.

P. aeruginosa is only moderately susceptible to levofloxacin or other fluoroquinolones, and nonpseudomonas nonfermenters also do not appear to be susceptible to levofloxacin. Anaerobes vary in susceptibility to levofloxacin, with *Bacteroides fragilis* strains ranging from susceptible to resistant, although *Clostridium perfringens* is susceptible. In contrast, Gram-negative bacteria, such as *Haemophilus influenzae, Moraxella catarrhalis* and *Legionella pneumophila*, and 'atypical' pathogens, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, are susceptible to levofloxacin and other fluoroquinolones.

Oral levofloxacin is 100% systemically available and its bioavailability is not affected by meals. Intravenous or oral routes of administration may be used interchangeably. The drug has linear pharmacokinetics over 50 to 1000mg doses. Steady state is reached after ≈3 days; the elimination half-life is 6.8 to 8.9 hours. ≈80% of a dose is found in the urine as unchanged drug and ≤5% as inactive *N*-oxide and demethyl metabolites within 24 hours. The active drug distributes well to target body tissues and fluids in the respiratory tract, skin, urine and prostate and its uptake by cells makes it suitable for use against intracellular pathogens. Dosages should be reduced in patients with renal failure, in whom

levofloxacin elimination is decreased. Old age and gender do not affect levofloxacin pharmacokinetics.

Clinical Use

Published and unpublished studies support the use of levofloxacin in patients with community-acquired pneumonia (CAP), acute maxillary sinusitis, acute exacerbations of chronic bronchitis (AECB), uncomplicated skin and soft tissue infections (SSTIs) or complicated urinary tract infections (UTIs, including acute pyelonephritis). Its efficacy has been demonstrated in a small number of comparative studies in each of these indications, supplemented by noncomparative trials in some indications. A total of >5600 patients in these trials were evaluated on at least 1 of the major outcome indicators: clinical cure rate, clinical success rate (clinical cure or improvement) and bacteriological eradication rate.

In patients with mild to severe CAP, oral levofloxacin 500 mg/day produced a similar clinical success rate (95.2%) to that seen with amoxicillin/clavulanic acid 1500/375 mg/day (95.3%) when these regimens were administered for 7 to 10 days in a double-blind study. In contrast, intravenous or oral levofloxacin 500 mg/day resulted in a statistically superior clinical success rate (96%) to that seen with the combined results of intravenous ceftriaxone 1 or 2 g/day or oral cefuroxime axetil 1000 mg/day (90%) after 7 to 14 days' treatment of patients with mild to severe CAP in a single-blind study. Patients with moderate to severe CAP achieved clinical cure and success rates of 65 and 87% after levofloxacin 500mg twice daily orally or intravenously and 55 and 86% after intravenous ceftriaxone 4000mg once daily. Bacteriological eradication was seen in 87 to 100% of patients receiving levofloxacin and in similar proportions of those receiving comparator agents (amoxicillin/clavulanic acid 97.5%; ceftriaxone and/or cefuroxime axetil 87%).

In AECB, oral levofloxacin 250 or 500mg once daily for 7 to 10 days was similar in efficacy to oral cefuroxime axetil 250mg twice daily for the same duration. Levofloxacin 500mg once daily was also equivalent in efficacy to cefuroxime axetil 250mg twice daily or cefaclor 250mg 3 times daily when given in shorter courses than its comparators (5 to 7 days *vs* 10 or 7 to 10 days). Clinical success and bacteriological eradication rates were similar between patients receiving levofloxacin (78 to 94.6% and 77 to 97%, respectively) and those receiving cefuroxime axetil (66 and 92.6%, and 68 and 95%, respectively) or cefaclor (92 and 87%, respectively).

When used for 10 to 14 days to treat radiologically confirmed acute maxillary sinusitis, oral levofloxacin 500mg once daily was similar in efficacy to oral amoxicillin/clavulanic acid 500mg/125mg 3 times daily or oral clarithromycin 500mg twice daily. Clinical cure rates with levofloxacin ranged from 58.3 to 63.2% (and were similar to that for amoxicillin/clavulanic acid, 58.6%). Bacteriological eradication rates in 2 noncomparative trials were 88.6 and 92%. Levofloxacin clinical success rates of 88.3 to 96% were also similar to those of amoxicillin/clavulanic acid (87.3%) and clarithromycin (93.3%).

When per-pathogen eradication rates were examined for respiratory pathogens detected in clinical trials, eradication rates with levofloxacin against *S. aureus*, *M. catarrhalis*, *E. coli*, *H. influenzae*, *H. parainfluenzae*, *K. pneumoniae*, *C. pneumoniae*, *M. pneumoniae* and *L. pneumophila* were very good to excellent and ranged from 89.1 to 100%. A lower eradication rate was seen for levofloxacin against *P. aeruginosa* (63%).

In patients with uncomplicated skin and soft tissue infections, oral levofloxa-

cin 500mg once daily for 7 to 10 days was similar in efficacy to oral ciprofloxacin 500mg twice daily. Clinical success occurred in 96.1 and 97.8% of levofloxacin recipients and 93.5 and 94.3% of ciprofloxacin recipients, whereas bacteriological eradication rates were 93.2 and 97.5% for levofloxacin and 88.8 and 91.7% for ciprofloxacin. Comparisons between levofloxacin and either ciprofloxacin or lomefloxacin in patients with complicated urinary tract infections also resulted in similar efficacy between these groups. Levofloxacin 250 mg/day for 10 days produced clinical success in 92 and 92.9% of patients and bacteriological eradications in 93.6 and 95.3%. The clinical success rates were 88% after ciprofloxacin 250mg twice daily for 10 days and 88.5% after lomefloxacin 400mg once daily for 14 days; bacteriological eradication rates were 97.5 and 92.1%, respectively.

Tolerability

Adverse events associated with levofloxacin are usually transient, mild to moderate in severity and generally similar to that of other fluoroquinolone agents. Nausea (1.1 to 3%) and diarrhoea (1.1. to 2.89%), are among the more common events seen after oral or intravenous use of the drug in clinical trials. Phlebitis and reddening at the infusion site may also occur with intravenous levofloxacin. According to an overview, the overall incidence of drug-related adverse events appears to be lower with levofloxacin (3.3%) than with the other fluoroquinolones ofloxacin (4.3%), ciprofloxacin (5.5 to 10.2%) or pefloxacin (8%).

Serious adverse events include rare cases of pseudomembranous colitis and haemolytic anaemia. The safety and efficacy of levofloxacin in children and adolescents below the age of 18 years have not been established. Fluoroquinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. Photosensitisation with levofloxacin is similar in incidence to that seen with ofloxacin and ciprofloxacin. CNS events such as seizures may be related to concurrent use of theophylline or nonsteroidal anti-inflammatory drugs and may occur less frequently with levofloxacin than ofloxacin.

Sucralfate and antacids that contain di- or trivalent cations may chelate with levofloxacin and thus limit its absorption. Cimetidine and probenecid may compete with levofloxacin for renal tubular secretion and thus prolong the half-life of levofloxacin. Both hyper- and hypoglycaemia have been reported in patients treated concomitantly with fluoroquinolones and an antidiabetic agent.

Dosage and Administration

Levofloxacin may be used to treat acute maxillary sinusitis, AECB, CAP, SSTIs or complicated UTIs (including pyelonephritis). The drug is available in both oral and intravenous dosage forms. European and US dosage guidelines for levofloxacin differ.

In the US, levofloxacin may be administered orally or intravenously for all indications. The usual dose of 500mg once daily may be used for acute sinusitis (administered for 10 to 14 days), AECB (7 days), CAP (7 to 14 days) and uncomplicated SSTIs (7 to 10 days). Levofloxacin 250mg once daily should be administered for 10 days to treat complicated UTIs or pyelonephritis.

In Europe, oral levofloxacin 500mg once daily is used to treat sinusitis (duration 10 to 14 days) and 250 to 500mg once daily is used for AECB (7 to 10 days). In patients with CAP, intravenous or oral levofloxacin 500mg once or twice daily is administered for 7 to 14 days. Levofloxacin 250mg once daily orally or intravenously may be used for 7 to 10 days in patients with complicated UTIs or pyelonephritis, but higher intravenous dosages may be considered for patients with severe disease. A 250mg once-daily or 500mg once- or twice-daily dosage

of oral levofloxacin may be administered for 7 to 14 days for SSTIs; if intravenous levofloxacin is used, 500mg twice daily is recommended.

Use of levofloxacin is contraindicated in children, adolescents, pregnant or breastfeeding women, and patients with epilepsy or a history of tendon disorders related to fluoroquinolones. Caution is warranted when patients with renal impairment receive levofloxacin concomitantly with probenecid or cimetidine; levofloxacin dosages should be adjusted according to creatinine clearance. Administration of sucralfate, iron salts or antacids containing magnesium or aluminium should be separated from levofloxacin administration by 2 hours.

1. Scope of the Review

Levofloxacin, a broad spectrum fluoroquinolone antibacterial agent, is the active optical *S*(–)-isomer of ofloxacin and has 2 to 4 times greater antibacterial activity than ofloxacin.[1] Levofloxacin was reviewed in *Drugs* in 1994,[1] but at that time, available clinical trials were limited to those conducted in Japanese patients who received lower levofloxacin dosages than are now used in Japan or elsewhere. In addition, comparative studies were conducted in only 2 indications, and compared levofloxacin only with ofloxacin.

Since the last review, results are available from studies in Western patients that examine the use of levofloxacin 250 to 1000 mg/day in comparison with other antibacterial agents. There have been separate clinical trial programmes in Europe and the US; efficacy results of those trials are combined in this review for an overall picture, although tolerability data from the 2 programmes are assessed separately. The purpose of this review is to assess the evidence for the efficacy and tolerability of levofloxacin in community-acquired pneumonia (CAP), acute maxillary sinusitis, acute exacerbations of chronic bronchitis (AECB), uncomplicated skin and soft tissue infections (SSTIs) and complicated urinary tract infections (UTIs; including pyelonephritis).

2. Pharmacology

2.1 Antibacterial Activity

Levofloxacin, like other fluoroquinolones, inhibits bacterial DNA gyrase, a type II topoisomerase.[1] It is active against a broad range of bacteria, including Gram-positive and Gram-negative, atypical and intracellular pathogens, but may have less activity against *Pseudomonas* spp. and many anaerobes.[1]

In this review, *in vitro* activity refers to minimum inhibitory concentrations (MICs) determined using agar or broth techniques and an inoculum size of 10^4 to 10^6 colony forming units (cfu) per millilitre of clinical isolates obtained worldwide. Broth or agar studies noting that National Committee for Clinical Laboratory Standards (NCCLS) guidelines from the US were followed were also included. In addition, because antibacterial susceptibility patterns can change with time, only studies published from 1993 onwards are used in this review, with the exception of a single earlier study of *Chlamydia pneumoniae*.[2] Only studies including ≥10 strains of each bacterial species are examined. Ordinarily, at least a 4-fold difference (≥2 dilutions) in median MICs needed to inhibit 90% of tested strains (MIC_{90}) is considered necessary to demonstrate a true difference in *in vitro* activity between levofloxacin and other antibacterial agents. However, consideration is also given to the relationship between median MIC_{90} values of agents and NCCLS interpretive guidelines for susceptibility. MIC_{90} values for relevant species are presented in table I.

In table I, levofloxacin is compared with ofloxacin, ciprofloxacin, sparfloxacin and trovafloxacin. Data on comparators were included only if they came from studies that also examined the activity of levofloxacin against the same species and isolates. Interpretive guidelines are required when considering MIC values in order to categorise the strains

Table I. *In vitro* antibacterial activity of levofloxacin (LVFX) and other fluoroquinolones. Studies used broth or agar dilution techniques and an inoculum size of 10^4 to 10^6 colony-forming units and included at least 10 clinical isolates. Median values are presented when ≥5 values were available; otherwise, single values or ranges are presented. References are presented by both drug and organism. References to the antibacterial activity of a specific drug against a particular organism are those which appear in the lists for relevant drug and organism

Organism	Median (or range) of MIC_{90} values in mg/L [no. of isolates] (range of MIC values)					References
	LVFX ≤2 mg/L[a]	OFX ≤2 mg/L[a]	CIP ≤1 mg/L[a]	SPAR[b]	TROV[b]	
Staphylococci						
Staphylococcus aureus (MS or OS)	0.5 [3174] (0.03-12.5)	0.5 [2976] (0.06->16)	0.75 [3115] (0.015-100)	0.12 [617] (0.015-25)	0.015-0.06[c] [112] (0.008-0.5)	3-18
S. aureus (MR or OR)	16 [1560] (≤0.03->128)	16 [1292] (0.015-128)	32 [1495] (0.06->128)	16 [612] (0.03-128)	1-8[c] [197] (0.015-≥64)	3-5, 7, 10-16, 18, 19
S. epidermidis (MS or OS)	1.25 [578] (0.06-128)	3 [496] (0.12-16)	1.5 [578] (0.03->16)	0.25 [355] (0.03-64)	0.13-4[c] [49] (0.03-4)	3, 4, 7, 8, 13, 16, 18, 20
S. epidermidis (MR or OR)	15 [1010] (0.1->100)	16 [954] (2-64)	16 [1010] (0.5-128)	8-100[c] [312] (0.05-100)	0.25-4[c] [36] (0.016-4)	3, 12-14, 16, 18, 20
S. saprophyticus (MS or uncharacterised)	≤0.5-0.5[c] [53] (0.25-1)	1-≤2[c] [33] (?)	0.5-1[c] [53] (0.25-1)		0.06[c] [20] (0.016-0.13)	3, 12, 16
S. saprophyticus (MR)	8[c] [20] (0.25-32)		16[c] [20] (0.25-64)		1[c] [20] (0.03-4)	3
Streptococci						
Streptococcus pneumoniae (PS)	1 [1051] (0.06-4)	2 [826] (0.5-8)	2 [928] (0.06->16)	0.5 [498] (0.06-0.5)	0.12-0.25[c] [184] (0.03-0.25)	3, 7, 11, 14, 17, 18, 21-25
S. pneumoniae (PI)	1 [395] (0.12-16)	2 [345] (0.5-4)	2 [395] (0.1-4)	0.12-0.5[c] [275] (0.06-16)	0.12-0.25[c] [170] (≤0.004-8)	3, 17, 18, 21, 22, 24, 25
S. pneumoniae (PR)	1 [341] (0.12->8)	2 [238] (0.5-4)	2 [274] (0.1-16)	0.25 [237] (0.031-4)	0.12 [115] (0.03-0.25)	3, 7, 11, 14, 17, 21-24, 26
S. pneumoniae (uncharacterised)	1 [3119] (0.05-4)	2 [3079] (0.5-8)	2 [3086] (<0.12->16)	0.375 [482] (≤0.12-1)	0.12-0.25[c] [1453] (0.03-0.25)	6, 10, 12, 13, 15, 27-36
S. pneumoniae (all strains)	1 [4906] (0.06-16)	2 [4488] (0.5-32)	2 [4653] (0.05->16)	0.25 [1492] (0.06-16)	0.12 [1922] (≤0.004-8)	3, 6, 7, 10-15, 17, 18, 21-36
S. pyogenes	1 [591] (0.06-16)	1 [469] (0.25->4)	1 [591] (0.12->16)	0.5 [332] (0.12->4)	0.06-0.25[c] [82] (0.03-1)	7, 10-15, 17, 18, 27, 29
Enterococci						
Enterococcus faecalis	2 [1133] (0.25->64)	6 [926] (1-≥32)	3.13 [1133] (0.25->64)	1 [529] (0.2-≥32)	2-16[c] [157] (0.06-16)	3, 4, 6, 11, 13-16, 18, 37
Enterobacteriaceae						
Citrobacter freundii	1 [428] (0.015-100)	1 [311] (0.015->16)	0.375 [337] (<0.008-100)	0.25-6.25 [51] (0.015->100)	0.25[c] [15] (0.015->16)	4, 10, 12-14, 16, 38
C. diversus	0.03 [121] (0.015-1)	0.06 [121] (0.015-2)	0.015 [121] (≤0.008-0.5)	0.25[c] [10] (0.015-0.25)	0.06[c] [10] (0.015-0.06)	4, 10, 12, 13, 16
Enterobacter aerogenes	0.35 [293] (0.015-4)	1 [254] (0.03-8)	0.055 [293] (0.008-2)	0.06-0.2[c] [55] (≤0.015-0.02)		4, 12-14, 16, 39
E. cloacae	0.5 [830] (0.006-≥32)	0.75 [627] (≤0.008-≥32)	0.185 [729] (0.003-≥32)	0.03-1[c] [119] (0.003-≥32)	0.06-1[c] [153] (0.008-16)	3, 4, 12-16, 38, 39
Escherichia coli	0.12 [4828] (≤0.008-256)	0.12 [4616] (0.004-64)	0.12 [4767] (0.004-128)	0.1-0.25[c] [141] (0.012-32)	0.03-32[c] [171] (0.008-256)	3, 4, 10, 12-14, 16, 33, 39
Klebsiella pneumoniae	0.5 [1408] (0.008-64)	1 [1278] (0.03-≥32)	0.25 [1408] (0.004-64)	0.12-1[c] [144] (≤0.015-≥32)	0.12-16[c] [186] (≤0.015-64)	3, 4, 12-17, 39
K. oxytoca	0.12 [265] (0.015-8)	0.12 [265] (≤0.03-4)	0.03 [265] (≤0.015-2)	0.06[c] [25] (≤0.015-2)	0.06[c] [25] (0.015-2)	4, 12, 13, 16, 39
Morganella morganii	0.2 [338] (0.006-1.56)	0.675 [218] (0.03->16)	0.06 [280] (0.004->8)	0.5-1[c] [90] (0.006-2)		4, 6, 10, 12, 14, 16, 38-40
Proteus mirabilis	0.16 [1052] (0.015-32)	0.25 [822] (0.03-8)	0.06 [949] (<0.008-4)	0.39-0.5[c] [115] (0.06-50)	0.5-0.5[c] [62] (0.06-8)	3, 4, 6, 10, 12-14, 16, 38, 39
P. vulgaris	0.12 [129] (0.015-1)	0.12-<2[c] [72] (0.03-2)	0.05 [129] (0.015-0.5)	0.39-0.5[c] [58] (0.06-1)		4, 6, 12, 14, 16

Table I. contd

Organism	Median (or range) of MIC_{90} values in mg/L [no. of isolates] (range of MIC values)					References
	LVFX ≤2 mg/L[a]	OFX ≤2 mg/L[a]	CIP ≤1 mg/L[a]	SPAR[b]	TROV[b]	
Providencia stuartii	0.5-32[c] [86] (0.006-64)	1-4[c] [45] (0.12-4)	0.12-2[c] [45] (0.025-2)			4, 12, 38
P. rettgeri	0.2-4[c] [60] (0.05-100)	4-4[c] [27] (0.06->16)	2-12.5[c] [60] (0.015->100)	12.5[c] [33] (0.05-100)		4, 14, 16
Serratia spp.	4 [815] (0.016-32)	4 [616] (0.06-16)	2 [715] (0.008-64)	0.5-50[c] [233] (0.015-100)	0.25-8[c] [125] (0.03-128)	3, 4, 10, 12-16, 38-40
Nonfermentative bacteria						
Pseudomonas aeruginosa	4 [3332] (0.025-128)	8 [2734] (0.03-64)	2 [3208] (≤0.008->100)	8 [363] (0.12-128)	2-16[c] [240] (≤0.015-64)	3, 4, 6, 7, 10, 12-17, 39-43
Nonpseudomonas nonfermenters	8[c] [410] (≤0.03->64)	32[c] [410] (≤0.03->64)	32[c] [410] (≤0.03->64)	8[c] [410] (≤0.03-64)		44
Other Gram-negative bacteria						
Acinetobacter spp.	4 [726] (0.015-64)	4 [606] (0.015-64)	2 [634] (0.008->256)	8 [299] (≤0.006-32)	0.03-16[c] [91] (≤0.015-32)	4, 10, 12-14, 16, 38-41, 44
Haemophilus influenzae	0.032 [776] (≤0.008->2)	0.0925 [514] (0.015-2)	0.016 [776] (0.004->2)	0.015 [588] (≤0.0015-0.125)	0.016-0.03[c] [454] (0.004->2)	3, 6, 7, 10, 14, 15, 17, 21, 45
Legionella pneumophila[d]	0.03-0.125[c] [150] (0.003-1)	0.015-0.25[c] [150] (0.06-1)	0.015-0.03[c] [94] (0.004-0.06)	0.002-0.015[c] [72] (0.002-0.03)		15, 40, 46, 47
Moraxella catarrhalis	0.06 [513] (≤0.03-0.25)	0.12 [360] (0.008-2)	0.03 [513] (≤0.002-0.5)	0.016 [401] (0.004-0.125)	0.015-0.03[c] [352] (≤0.002-0.3)	3, 4, 6, 7, 14, 15, 17, 21
Anaerobes						
Bacteroides fragilis	1-16[c] [123] (0.5-16)	16[c] [70] (?)	2-16[c] [105] (2-32)	1-4[c] [85] (0.5-4)	1[c] [38] (0.12-8)	3, 6, 40, 48
Clostridium perfringens	0.5-1[c] [86] (0.06-4)	0.5[c] [52] (?)	0.5[c] [52] (?)	0.25[c] [52] (?)	0.12[c] [11] (0.03-0.25)	18, 38, 48
Other anaerobes	8[c] [317] (≤0.008->128)				1[c] [317] (≤0.008->16)	48
'Atypical' bacteria						
Chlamydia pneumoniae[de]	0.05[c] [11] (0.125-0.5)					2
Mycoplasma pneumoniae[de]	0.5[c] [77] (0.025-0.5)	1[c] [43] (0.5-1)		0.063[c] [43] (0.031-0.063)		49
References	2-49	4, 5, 8-13, 15-18, 20-22, 24, 25, 27-30, 32-36, 39-41, 44-47, 49	3, 4, 6-22, 24, 25, 27-30, 32, 34-37, 39-42, 44, 45, 47, 50	6-9, 11, 13-15, 18-21, 24, 26, 27, 30, 35, 40, 41, 44, 45, 49	3, 13, 15, 19, 21, 27, 32, 41, 48	

a Recommended susceptibility breakpoints, except for *H. influenzae* (susceptible at LVFX and OFX MICs of ≤2 mg/L and CIP MICs of ≤1 mg/L) and *S. pneumoniae* (susceptible, intermediate and resistant at LVFX and OFX MICs of ≤2, 4 and ≥8 mg/L).[51]

b Susceptibility breakpoints are not available for these antibacterial agents.

c Single value is from a single study; a range of values is from fewer than 5 studies.

d Susceptibility breakpoints are not available for these bacteria; no median values are available for these organisms, due to the limited numbers of published studies.

e Tested in cell culture.

CIP = ciprofloxacin; **MIC** = minimum inhibitory concentration; **MIC_{90}** = minimum concentration required to inhibit 90% of strains; **MR** = methicillin-resistant; **MS** = methicillin-susceptible; **OFX** = ofloxacin; **OR** = oxacillin-resistant; **OS** = oxacillin-susceptible; **PI** = penicillin-intermediate; **PR** = penicillin-resistant; **PS** = penicillin-susceptible; **SPAR** = sparfloxacin; **TROV** = trovafloxacin; **?** = unknown.

as susceptible, intermediate or resistant. MIC breakpoints for levofloxacin according to NCCLS guidelines are ≤2 mg/L (susceptible), 4 mg/L (intermediate) and ≥8 mg/L (resistant).[51] For *Haemophilus influenzae* , the NCCLS susceptibility breakpoint for levofloxacin is ≤2 mg/L and for *Streptococcus pneumoniae* the breakpoints are ≤2 mg/L (susceptible), 4 mg/L (intermediate) and ≥8 mg/L (resis-

tant).[51] Where available, NCCLS breakpoints for the comparative agents are listed in table I. For information on achievable peak plasma concentrations (C_{max}) of levofloxacin and the comparator agents, see section 2.3.1.

2.1.1 Staphylococci

Methicillin- or oxacillin-sensitive *Staphylococcus aureus, S. epidermidis* and *S. saprophyticus* were susceptible to levofloxacin, with the highest median MIC_{90} value being 1.25 mg/L for any of these strains (table I).

Against staphylococci, levofloxacin appears to have activity that is similar to or greater than that of some older fluoroquinolones (ofloxacin and ciprofloxacin), but may be less active than some newer fluoroquinolones. The activity of levofloxacin was similar to that of ciprofloxacin and ofloxacin against methicillin- or oxacillin-susceptible *S. aureus* and *S. saprophyticus*, since all median MIC_{90} values were within 4-fold (2 dilutions) of each other. MIC_{90} values for methicillin- or oxacillin-susceptible *S. epidermidis* were below the susceptibility breakpoint for levofloxacin (≤2 mg/L susceptible, median MIC_{90} 1.25 mg/L), but these organisms were only intermediately susceptible to ofloxacin (≤2 mg/L susceptible, median MIC_{90} 3 mg/L) or ciprofloxacin (≤1 mg/L susceptible, median MIC_{90} 1.5 mg/L) [table I].[51] Susceptibility breakpoints were not available for the newer fluoroquinolones sparfloxacin and trovafloxacin, and these agents were tested against much smaller numbers of isolates than levofloxacin, making comparisons less certain. However, medians or ranges of MIC_{90} values for sparfloxacin and trovafloxacin tended to be >4-fold smaller than those of levofloxacin for methicillin- or oxacillin-susceptible staphylococci (table I).

Mutations to both DNA topoisomerase II subunit A (gyrA) and DNA topoisomerase IV grlA subunits are thought to be needed to produce high-level resistance of *S. aureus* to fluoroquinolones.[52] Selection of 1-step mutants appears to occur less often with levofloxacin or ofloxacin than with ciprofloxacin, sparfloxacin or pefloxacin.[53,54] Levofloxacin, unlike ciprofloxacin, did not select for *S. aureus* resistance in rats *in vivo*.[55] *In vitro* selection of fluoroquinolone resistance of *S. aureus* occurred significantly less frequently with levofloxacin than with ciprofloxacin.[55,56]

With regard to staphylococci examined in this review, *S. aureus, S. epidermidis* or *S. saprophyticus* that were resistant to methicillin or oxacillin were also resistant to levofloxacin, which had median or single MIC_{90} values of 16, 15 and 8 mg/L, respectively, against these agents (table I). These bacteria are similarly resistant to ofloxacin and ciprofloxacin. The comparative activity of levofloxacin and either sparfloxacin or trovafloxacin against these resistant strains is more difficult to determine because of the small numbers of studies and lack of susceptibility breakpoints for the newer drugs. Current evidence suggest little difference between levofloxacin and sparfloxacin, but possibly greater activity of trovafloxacin compared with levofloxacin against methicillin- or oxacillin-resistant staphylococci (table I).

2.1.2 Streptococci and Enterococci

Levofloxacin is active against penicillin-susceptible, -intermediate and -resistant strains of *S. pneumoniae* (table I). There are no apparent differences in susceptibility to levofloxacin of these characterised strains or of other strains whose penicillin susceptibility was not characterised; all had median MIC_{90} values of 1 mg/L. Furthermore, the range of MICs achieved in studies of these 4906 isolates has been confirmed by a large surveillance study examining 9145 clinical isolates (range of MIC values ≤0.002->32 mg/L) that used the Etest method (a commercial disc diffusion method).[57]

The activity of levofloxacin and other fluoroquinolones against all strains of *S. pneumoniae*, when compared on the basis of a 2-dilution difference from the median levofloxacin MIC_{90} is shown in figure 1a. According to this representation, levofloxacin appears to be 2-fold more active than ofloxacin or ciprofloxacin against *S. pneumoniae*. However, sparfloxacin and trovafloxacin, although not tested in as many clinical isolates, appear to be more active than levofloxacin. Susceptibility breakpoints are not yet established for

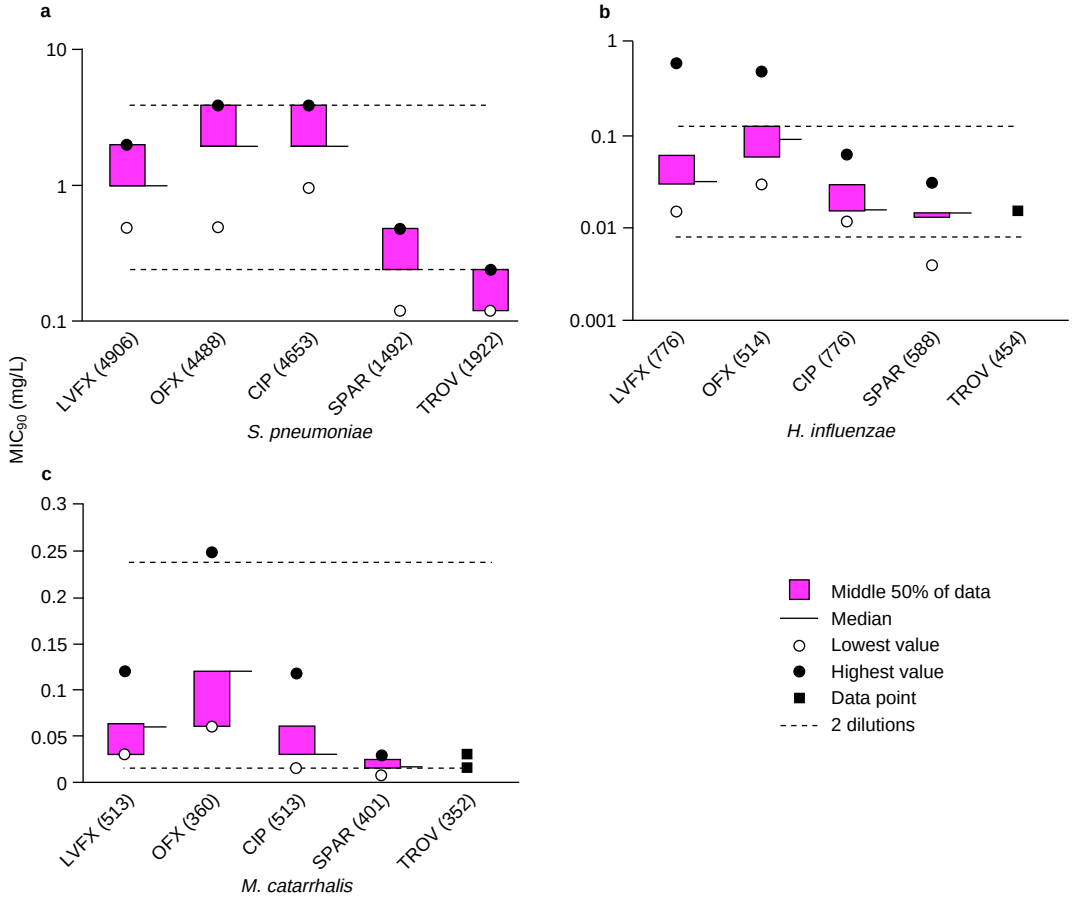

Fig. 1. Antibacterial activity of levofloxacin (LVFX) and other fluoroquinolones against key pathogens of the respiratory tract. Minimum inhibitory concentrations against 90% of isolates (MIC_{90}) are presented as boxplots on a logarithmic scale, with the median value, middle 50% of data points and upper and lower extremes of data marked. Agents are considered to have greater or lesser activity than LVFX if their median MIC_{90} is outside the area noted by the lines (which indicate 2 dilutions from the median LVFX MIC_{90}). Numbers of isolates tested are listed in parentheses alongside the name of the agent. For comparator agents, when there were ≤4 values, the individual data points were listed rather than medians. (a) *Streptococcus pneumoniae*;[3,6,7,10-15,17,18,21-36] (b) *Haemophilus influenzae*;[3,6,7,10,14,15,17,21,45] (c) *Moraxella catarrhalis*.[3,4,6,7,14,15,17,21] **CIP** = ciprofloxacin; **OFX** = ofloxacin; **SPAR** = sparfloxacin; **TROV** = trovafloxacin.

sparfloxacin or trovafloxacin, and none exist for ciprofloxacin against *S. pneumoniae*,[51] so comparisons of these agents with levofloxacin on the basis of NCCLS breakpoints is not possible at present. Ofloxacin shares the same susceptibility breakpoint for *S. pneumoniae* as levofloxacin (≤2 mg/L), but levofloxacin MIC_{90} values were all at or below this breakpoint, whereas those for ofloxacin were all at or above it (fig. 1a).

Active efflux is a mechanism of resistance to the fluoroquinolones in *S. pneumoniae*. In 1 study, levofloxacin appeared to be a less active substrate for a bacterial efflux pump in this pathogen.[58] Levofloxacin also appeared to be less likely than ciprofloxacin or ofloxacin to select resistant mutants of *S. pneumoniae*.[22]

S. pyogenes appear to be susceptible to levofloxacin and ofloxacin, and there were no differences in susceptibility of these bacteria between

levofloxacin and sparfloxacin (table I). Because of the overlap between a 4-fold difference from the median levofloxacin MIC_{90} and the range of trovafloxacin MIC_{90} values, it is difficult to characterise the difference between susceptibility of *S. pyogenes* to these 2 agents without more data.

The median MIC_{90} of levofloxacin against *Enterococcus faecalis* was 2 mg/L, making it similar in activity to ciprofloxacin and sparfloxacin, but superior in activity to ofloxacin (table I). Although *E. faecalis* was susceptible to levofloxacin, it was only intermediately susceptible to ofloxacin or ciprofloxacin (table I).

2.1.3 Enterobacteriaceae

Most Enterobacteriaceae examined in this review were susceptible to levofloxacin (table I). These included *Enterobacter cloacae*, *E. aerogenes*, *Citrobacter freundii*, *C. diversus*, *Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca*, *Morganella morganii*, *Proteus mirabilis* and *P. vulgaris*, for which the highest median MIC_{90} was at the breakpoint for susceptibility to levofloxacin (2 mg/L). Against most of these species, the activity of levofloxacin was similar to that of ciprofloxacin or ofloxacin; an exception is *E. aerogenes*, against which ciprofloxacin (median MIC_{90} 0.055 mg/L) was more active than levofloxacin (median MIC_{90} 0.35 mg/L, ≥4-fold greater than that for ciprofloxacin) [table I]. Comparisons between levofloxacin and either sparfloxacin or trovafloxacin are hampered by a lack of data in many instances, and although the activity of these 3 agents appeared to be generally similar against these bacteria, levofloxacin may be more active than sparfloxacin against *C. diversus* (table I).

However, resistance of Enterobacteriaceae to the fluoroquinolones appears to be a growing problem,[59] with many examples of resistance being evident. Only small numbers of studies were available relating to *Providencia stuartii* or *P. rettgeri*, but MIC_{90} values ranged from susceptible to resistant for levofloxacin, ofloxacin, ciprofloxacin and sparfloxacin.[4,12,14,16,38] *Serratia* spp. tested were only intermediately susceptible to levofloxacin, ofloxacin or ciprofloxacin (table I). *K. pneumoniae* isolates (n = 25) that were resistant to ceftazidime (MIC ≥16 mg/L) were also resistant to levofloxacin (MIC_{90} 16 mg/L), ciprofloxacin (8 mg/L) and trovafloxacin (16 mg/L).[3] When 91 ampicillin- or ceftazidime-resistant (MIC ≥16 mg/L) *E. coli* isolates were examined separately, these were found to be resistant to levofloxacin, ciprofloxacin and trovafloxacin; MIC_{90} values were 8 to 16 mg/L for levofloxacin, 4 to 16 mg/L for ciprofloxacin and 8 to 32 mg/L for trovafloxacin.[3]

2.1.4 Other Gram-Negative Bacteria

H. influenzae and *Moraxella catarrhalis* are susceptible to levofloxacin, with median MIC_{90} values of 0.032 mg/L (776 isolates) and 0.06 mg/L (513 isolates), respectively (fig. 1b and 1c). Both β-lactamase–positive and –negative *H. influenzae*[3,6,7,10,14,15,17,21,45] and *M. catarrhalis* were susceptible to levofloxacin, and there were no major differences between the activity of levofloxacin, ofloxacin, ciprofloxacin, sparfloxacin or trovaloxacin against these pathogens. The MIC ranges determined in 776 *H. influenzae* isolates and 513 *M. catarrhalis* isolates (table I) have been confirmed recently by the Etest method in 1571 *H. influenzae* (≤0.002-2.0 mg/L) and 606 *M. catarrhalis* (≤0.002-0.75 mg/L) clinical isolates.[57]

Levofloxacin is also active against *Legionella pneumophila*. MIC_{90} values for levofloxacin against *L. pneumophila* ranged from 0.03 mg/L to 0.125 mg/L,[15,46,47] with an overall range of MIC values from 0.003 to 1 mg/L. These MIC_{90} values were within two 2-fold dilutions of those for ofloxacin (0.015 to 0.25 mg/L), ciprofloxacin (0.015 to 0.03 mg/L) and sparfloxacin (0.002 to 0.015 mg/L).[15,46,47]

2.1.5 Nonfermentative Bacteria

Pseudomonas aeruginosa is, at best, moderately susceptible to levofloxacin, with a median MIC_{90} value of 4 mg/L against a total of 3332 isolates (table I). Other fluoroquinolones examined do not appear to differ greatly from levofloxacin in activity against *P. aeruginosa* (table I). If evidence from a collection of nonpseudomonas nonfermenters is confirmed, these bacteria are not susceptible to

levofloxacin or to other fluoroquinolones examined (table I).

2.1.6 Anaerobes

Anaerobes appear to have varying susceptibility to levofloxacin; isolates of *Bacteroides fragilis* ranged from fully susceptible to resistant (table I). *B. fragilis* strains tested were resistant to ofloxacin and intermediately susceptible or resistant to ciprofloxacin. There are no susceptibility breakpoints for sparfloxacin or trovafloxacin, and few data relate to these 2 antibacterial agents, making between-drug comparisons unreliable. *Clostridium perfringens* is susceptible to levofloxacin, with MIC_{90} values of 0.5 to 1 mg/L against 86 isolates (table I). These MIC_{90} values are similar to those seen with ofloxacin (0.5 mg/L against 52 isolates), ciprofloxacin (0.5 mg/L, n = 52), sparfloxacin (0.25 mg/L, n = 52) and trovafloxacin (0.12 mg/L, n = 11).[18,38,48]

2.1.7 'Atypical' Pathogens

Levofloxacin is active against *C. pneumoniae* and *Mycoplasma pneumoniae* (table I). 11 clinical isolates of *C. pneumoniae* were susceptible to levofloxacin (MIC_{90} 0.05 mg/L) in a 1992 study.[2] Levofloxacin, ofloxacin and sparfloxacin were all active against *M. pneumoniae* isolates;[49] MIC_{90} values were: levofloxacin 0.5 mg/L (n = 43), ofloxacin 1 mg/L (n = 43) and sparfloxacin 0.063 mg/L (n = 43).

2.2 Bactericidal and Postantibiotic Effects

The minimum bactericidal concentration (MBC) of levofloxacin has been shown to be the same as the MIC for *E. coli*, *P. aeruginosa* and *S. aureus*.[1] The drug also had bactericidal effects against *S. epidermidis* and *E. faecalis*,[1] and against *K. pneumoniae*,[60] *S. pneumoniae*,[61-63] *L. pneumophila*[46,47] and several anaerobes.[64] Against *S. pneumoniae*, *in vitro* bactericidal activity of levofloxacin at its optimal bactericidal concentration (the single concentration at which maximum kill is achieved in a biphasic dose-response) was greater than that of ofloxacin, ciprofloxacin or sparfloxacin.[65]

Levofloxacin has been shown to have a postantibiotic effect (PAE) against *S. epidermidis*, *E. faecalis* and *E. coli*.[1] A PAE has now also been shown against *B. fragilis*,[66] *S. aureus* and *S. pneumoniae*,[67-69] and has been postulated against *L. pneumophila* on the basis of the ability of levofloxacin pretreatment to inhibit regrowth of the bacterium.[70]

2.3 Pharmacokinetic Properties

The pharmacokinetics of levofloxacin have been studied in patients with various bacterial infections, healthy volunteers and volunteers with renal failure, and were previously reviewed by Davis and Bryson[1] and Fish and Chow.[71] These 2 reviews form the basis of this assessment.

Although absorption of levofloxacin is slightly delayed by food, its overall bioavailability is not altered by a high-fat meal.[72] In addition, infectious diseases did not affect pharmacokinetic results.[71] Values of levofloxacin pharmacokinetic parameters for fasting and nonfasting healthy volunteers are combined in table II. The table contains data on 250, 500 and 1000mg single and multiple doses.

2.3.1 Overview of Pharmacokinetic Properties

Levofloxacin is 100% bioavailable after oral administration,[73] making it possible to administer the drug at the same dosages either orally or intravenously. It exhibits linear pharmacokinetics over the dosage range from 50 to 1000mg, with an area under the plasma concentration-time curve (AUC) of 4.7 mg/L · h after a 50mg oral dose and 111 mg/L · h after a 1000mg dose.[1,71] With an elimination half-life of 6.8 to 7.6 hours after single or multiple doses of levofloxacin 500mg orally or intravenously,[73] plasma concentrations reach steady state after about 3 days.

The C_{max} of levofloxacin achieved after single 500mg oral doses ranged from 4.5 to 5.2 mg/L (table II). For comparator agents examined in table I, single dose C_{max} values were as follows: ofloxacin 400mg, 4.8 mg/L;[77] ciprofloxacin 750mg, 2.0 to 3.4 mg/L;[78] sparfloxacin 400mg, 1.1 to 1.6 mg/L;[79] trovafloxacin 200mg, 2.9 mg/L.[80] C_{max} values at steady state after dosages of 500mg once

Table II. Mean pharmacokinetics of levofloxacin in healthy volunteers[73-76]

Dose (mg)	No. of volunteers	C_{max} (mg/L)	t_{max} (h)	AUC (mg/L • h)	$t_{½β}$ (h)	Vd (L/kg)	CL (L/h)	f_e (%)
Single doses								
Oral administration								
250	15	2.8	1.6	27.2	7.3		9.36	87.7
500	33	4.5-5.2	1.3-1.6	43.2-47.7	6.8-7.4	1.28	10.5-11.9	64-102
1000	10	8.85	1.7	111	7.9	1.24	9.36	73
Intravenous administration								
500	10	6.3	1.0	55.3	7.1	0.94	9.4	60
Multiple doses (steady state)								
Oral administration								
500 od	10	5.7	1.1	47.5	7.6	1.35	10.5	67
500 bid	20	7.8	1.3	59.0	8.4	1.34	8.6	72
1000 od	10	11.8	1.7	118	8.9	1.35	8.76	71
Intravenous administration								
500 od	10	6.4	1.0	54.6	7.0	0.96	9.5	63
500 bid	10	7.9	1.0	49.6	7.6	1.47	10.2	68

AUC = area under the plasma concentration-time curve; **bid** = twice daily; **CL** = clearance; **C_{max}** = peak plasma concentration; **f_e** = fraction of drug excreted unchanged in the urine; **od** = once daily; **t_{max}** = time to reach C_{max}; **$t_{½β}$** = terminal elimination half-life; **Vd** = volume of distribution.

or twice daily or 1000mg once daily are shown in figure 2.

Renal excretion is primarily responsible for the elimination of levofloxacin. Following oral administration, 70.6% of the dose was recovered in the urine as unchanged drug within 24 hours,[71] and 2% was recovered unchanged in faeces.[1] Levofloxacin is metabolised in the liver to demethyllevofloxacin and levofloxacin-*N*-oxide.[71] These metabolites make up ≤5% of a dose excreted in the urine within 24 hours.[71] Since formation of the metabolites is negligible, they have little relevant physiological activity.[75]

Levofloxacin is generally well distributed to body tissues and fluids, except that it penetrates poorly into the CNS.[71] The drug is 24 to 38% bound to plasma protein. Levofloxacin, like ofloxacin, is thought to cross the placenta and be secreted into breast milk.[71] It is taken up into polymorphonuclear leucocytes by a passive mechanism that rapidly results in cellular to extracellular ratios of about 6, making it suitable for use against intracellular organisms.[81-83] There is excellent distribution of levofloxacin to tissues and fluids of the respiratory tract and skin and it is found in large quantities in the urine. Tissue and fluid concentrations of levofloxacin exceed those in plasma at most sampling sites relevant to the infections examined in this review (table III). Although levofloxacin concentrations are lower in the ethmoid sinus, bronchoalveolar fluid, bronchial lavage fluid and blister fluid than in plasma, levofloxacin concentrations in the lung, maxillary sinus, skin, sputum, and in alveolar macrophages and epithelial lining fluid exceed those in plasma by ratios of

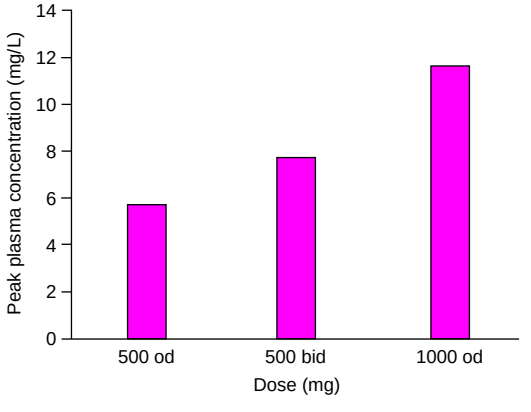

Fig. 2. Peak plasma concentrations of levofloxacin at steady state after once (od)- or twice (bid)-daily 500mg doses or 1000mg once daily.[73-76]

1.14 to 11.6 (table III). Levofloxacin concentrations are also high in the urine.

2.3.2 Pharmacokinetics in Special Populations

Dosage reductions should be considered for patients with renal impairment (see section 5.3), but the drug is not substantially removed by dialysis, so no dose supplement should be given after haemo- or peritoneal dialysis.[85] Peak plasma levofloxacin concentrations (C_{max}) are unaffected by renal failure, but renal clearance of the drug is reduced from 3.4 to 0.78 L/h (57 to 13 ml/min) as creatinine clearance decreases from a range of 3 to 4.8 L/h to <1.14 L/h.[85]

Neither age *per se* nor gender affected the pharmacokinetics to any clinically significant extent.[86] Differences in levofloxacin pharmacokinetic parameters between older and younger healthy volunteers could be accounted for by reduced renal function in the elderly patients.

2.3.3 Pharmacokinetic-Pharmacodynamic Relationships

Clinical and microbiological outcomes of levofloxacin therapy can be predicted by the site of infection (with UTIs being most responsive to treatment) and the ratio of C_{max} to the MIC.[87] In the 313 patients with respiratory, skin or urinary tract infections treated with levofloxacin for whom MIC and/or pharmacokinetic data were available, the median C_{max} to MIC ratio was 12.1. Clinical cure or improvement was seen in 99% of patients with a C_{max} : MIC ratio of >12.2, and in 83% of those with a ratio of ≤12.2.[87]

3. Clinical Use

Evidence for the efficacy of levofloxacin in Western patients with CAP, acute maxillary sinusitis, AECB, uncomplicated SSTIs and complicated UTIs (including pyelonephritis) comes from non-comparative and controlled comparative trials. Some studies evaluated in this review have been published only as abstracts or are unpublished and available only from the manufacturer as data on file. In addition, controls for bias were less than ideal in many studies; many comparative studies, although randomised, did not involve blinding of investigators or patients.

Major outcome measures used to assess response in clinical trials of antibacterial agents include clinical cure or clinical success and bacteriological eradication. Usually, 'clinical cure' is said

Table III. Distribution of levofloxacin to relevant tissues and fluids. Data are from the review of Fish and Chow[71] unless otherwise specified

Body fluid or tissue	Dose (mg) [no. samples/hours postdose]	Plasma concentration (mg/L)	Tissue/fluid concentration (μg/g or mg/L)	Tissue or fluid : plasma concentration ratio
Alveolar macrophages[84]	500 [?/4]	4.1	27.7	6.8
	500 [?/12-24]	1.2	13.9	11.6
Blister fluid	500 [6/0.5-2.4]	5.0	4.7	0.94
Bronchial lavage fluid	200 [7/1-3]	2.52	0.12	0.06
Bronchoalveolar lavage fluid	200 [8/1-3]	2.52	0.21	0.1
Epithelial lining fluid[84]	500 [?/4]	4.1	10.9	3.0
	500 [?/6-8]	4.0	10.1	2.7
Ethmoid sinus	100 [2/1]	0.84	0.67	0.63
Lung	500 [3/4-6]	2.93	11.28	5.02
	500 [3/21-25]	0.72	2.43	4.13
Maxillary sinus	100 [41/1-8]	0.45	0.67	1.15
Prostate gland	100 [23/1-6]	0.90	1.15	1.28
Skin	200 [39/0.8-4]	1.73	1.85	1.14
Sputum	100 [2/4]	1.10	1.27	1.15
Urine	500 [10/0-12]		309-343	
	500 [10/12-24]		128-131	

to occur in patients with complete resolution of signs and symptoms and 'clinical success' occurs in patients with clinical cure or pronounced improvement, and this was generally assessed 2 to 10 days after the end of treatment. In patients with pneumonia, improvement on chest x-rays was an additional sign of clinical cure. 'Bacteriological eradication' rates include patients in whom pathogens found at study entry are eradicated at the end of the study, although sometimes per-patient data were unavailable and per-pathogen eradication rates were used instead. Relapse is defined as reappearance of or deterioration in signs and symptoms of infection and although usually assessed ≈4 weeks after the end of treatment, the time of assessment varied in clinical trials. Intention-to-treat data were available for only a few studies, so per-protocol data were generally used to make comparisons across studies.

Over 5600 patients were evaluated for efficacy in studies of levofloxacin. In this section, the clinical and bacteriological results of these studies are examined within each indication.

3.1 Respiratory Tract Infections

3.1.1 Community-Acquired Pneumonia

Levofloxacin 500 mg/day was as effective as amoxicillin/clavulanic acid (1500/375 mg/day) and more effective than ceftriaxone 1000 to 2000 mg/day (with or without cefuroxime axetil 1000 mg/day) when used to treat patients with mild to severe CAP (table IV). Levofloxacin 500 to 1000 mg/day was also as effective as ceftriaxone 4000 mg/day in patients with moderate to severe CAP. Increasing the dose of levofloxacin to 1000 mg/day from 500 mg/day did not result in increased efficacy.

Clinical Cure or Success Rates

Intravenous and/or oral levofloxacin 500mg once or twice daily for 5 to 14 days produced clinical cure rates of 52.4 to 77.8% and clinical success rates of 87 to 96% in comparative and noncomparative trials in patients with mild to severe CAP (table IV). Respective clinical cure and success rates for its comparators were as follows: amoxicillin/clavulanic acid 53 and 95.3%, ceftriaxone 55 and 86% and cefuroxime axetil/ceftriaxone (clinical success only) 90% (table IV). In 1 study, the clinical cure and success rates with levofloxacin were superior to those with ceftriaxone (95% confidence intervals for differences in clinical cure: –25.6, –6.1; clinical success: –10.7, –1.3).[88]

Clinical relapse rates were similarly low in levofloxacin and cefuroxime axetil/ceftriaxone groups (2.8 *vs* 1.9%)[88] and relapse occurred in similar percentages of levofloxacin recipients in this comparative trial and in the noncomparative trial (2.6%).[93]

Bacteriological Eradication Rates

Overall eradication rates with oral or intravenous levofloxacin ranged from 87 to 100% (table IV). Only one-third to two-thirds of patients evaluable for clinical success were evaluable for bacteriological eradication. Rates of bacteriological eradication ranged from 97.8 to 100% after oral levofloxacin 500mg once or twice daily for 7 to 10 days,[89,90] and were similar to those after oral amoxicillin 500mg plus clavulanic acid 125mg 3 times daily for 7 to 10 days (97.5%).[89,90] When oral or intravenous levofloxacin 500mg was administered once daily for 7 to 14 days, the bacteriological eradication rates in different studies were 95.1%[93] and 98%.[88] In the latter study, the comparator agents oral cefuroxime axetil or intravenous ceftriaxone for 7 to 14 days produced bacteriological eradication in 85% of the subset of patients with typical pathogens[88] and 90.4% across all pathogens.[94] In the published report of that trial,[88] where eradication rates were assessed only in patients with typical pathogens, the difference in eradication rates between these groups suggested superiority of levofloxacin compared with cefuroxime axetil or ceftriaxone (95% confidence interval for the difference –21.6 to –4.8%). An unpublished study[91,92] comparing intravenous and oral levofloxacin with intravenous ceftriaxone for at least 5 days found eradication rates of 87% in both groups.

Superinfections were noted in a total of 9 levofloxacin recipients and 13 patients receiving the comparator agents in the 3 comparative trials.[88,90,92]

Table IV. Therapeutic efficacy of levofloxacin (LVFX) in adult patients with community-acquired pneumonia

References	Study design/ disease severity	Dosage (mg)	Treatment duration (days)	Clinical cure rate (%)[a]	Clinical success rate (%)[a]	Bacteriological eradication rate (%)[b]	Relapse rate (%)[c]	Overall efficacy
Comparative trials								
File et al.[88]	r, nb, pg, mc, PP, mild to severe	LVFX 500 od IV and/or PO	7-14		218/226 (96)	See text	2.8	LVFX > CRO and/or CXM[e]
		CXM 500 bid PO and/or CRO 1000-2000 od or bid IV[d]	7-14		208/230 (90)	See text	1.9	
Carbon et al.;[89][f] data on file[90]	r, db, dd, mc, pg, PP, 'nonsevere'	LVFX 500 od PO	7-10	76/145 (52.4)[g]	138/145 (95.2)	44/45 (97.8)		LVFX 500 ≡ LVFX 1000 ≡ AMC
		LVFX 500 bid PO		78/147 (53.1)[g]	137/147 (93.8)	53/53 (100)		
		AMC 500/125 tid PO		79/149 (53.0)[g]	141/149 (95.3)	39/40 (97.5)		
Norrby et al.;[91][f] data on file[92]	r, nb, mc, pg, PP, moderate to severe	LVFX 500 bid IV × 3-5 days, then 500 bid PO or 250 bid PO	≥5[h] (median 9)	82/127 (65)	111/127 (87)	71/82 (87)		LVFX ≡ CRO
		CRO 4000 od IV	≥5 (median 8)	77/139 (55)	120/139 (86)	92/106 (87)		
Noncomparative trial								
Data on file[93]	nb, mc, mild to severe	LVFX 500 od IV or PO	7-14	182/234 (77.8)	222/234 (94.7)	155/163 (95.1)	4/152 (2.6)	

a Where defined, clinical cure indicated resolution of clinical signs and symptoms (and improvement in chest x-rays) and clinical success indicated clinical cure plus pronounced improvement; assessed 2 to 5 days,[92] 2 to 10 days[89,90] or 5 to 7 days[88,93] after treatment.

b Bacteriological eradication indicated elimination of pathogenic bacteria at the end of treatment; rates are based on numbers of patients with pathogenic species after treatment *vs* pretreatment or on per-pathogen eradication rates (in which there may be >1 pathogen per patient).

c Relapse was assessed 21 to 28 days after treatment.

d IV or PO erythromycin or doxycycline could be added if 'atypical pathogens' were present or suspected.

e 95% confidence intervals for differences in clinical cure (–25.6, –6.1), clinical success (–10.7, –1.3) and bacterial eradication (–21.6, –4.8) rates show superiority of LVFX over comparators.

f Reported as an abstract.

g Responses of 30 patients (10 LVFX 500, 12 LVFX 1000, 8 AMC) were classed as failure because their post-therapy visit occurred 'too early' (≤2 days after the end of treatment).

h Administration was switched from IV to PO after a median of 4 days.

AMC = amoxicillin/clavulanic acid; **bid** = twice daily; **CRO** = ceftriaxone; **CXM** = cefuroxime axetil; **db** = double-blind; **dd** = double-dummy; **IV** = intravenous; **mc** = multicentre; **nb** = nonblind; **od** = once daily; **pg** = parallel group; **PO** = oral; **PP** = per-protocol efficacy data; **r** = randomised; **tid** = 3 times daily; ≡ indicates equal efficacy between 2 agents; **>** denotes superior efficacy with former compared with latter agent.

Two of the 9 bacteria found in levofloxacin patients were resistant to this drug (1 *P. aeruginosa* and 1 *Klebsiella* spp.), whereas 4 of the 13 bacteria found in recipients of the comparator drugs were resistant to those agents. For a further evaluation of microbiological data on a per-pathogen basis, see section 3.1.4.

3.1.2 Acute Exacerbations of Chronic Bronchitis

In patients with AECB levofloxacin 250 or 500 mg/day for 5 to 10 days was similar in efficacy to cefuroxime axetil 250mg twice daily for 7 to 10 days or cefaclor 250mg 3 times daily for 7 to 10 days (table V). From results of 2 studies,[95,96] it also appeared that levofloxacin achieved similar efficacy with a shorter duration of therapy (5 to 7 days) than was used with comparator agents (7 to 10 days), although short-duration regimens with the comparators were not tested.

Clinical Success Rates

In the largest study,[97] clinical success rates were 78 and 79% with levofloxacin 250 and 500 mg/day regimens and 66% for the cefuroxime axetil group.

No statistically significant difference between these groups was noted. In the other 2 studies, clinical success rates with levofloxacin 500 mg/day (94.6%[95] and 92%[96]) were similar to those for the cefuroxime axetil (92.6%)[95] and cefaclor (92%)[96] groups.

Bacteriological Eradication Rates

Bacteriological eradication rates were similar between all levofloxacin regimens (77 to 97%) and corresponding comparator agents (cefuroxime axetil 68%[97] and 95%[95], cefaclor 87%[96]) in treatment arms examining from 89 to 222 patients. For a further evaluation of microbiological data on a per-pathogen basis, see section 3.1.4.

3.1.3 Acute Maxillary Sinusitis

In comparative trials in patients with acute maxillary sinusitis, oral levofloxacin 500 mg/day was similar in efficacy to oral amoxicillin/clavulanic acid 500mg/125mg 3 times daily or oral clarithromycin 500mg twice daily (table VI).

Rates of clinical cure with levofloxacin in comparative and noncomparative studies ranged from 58.3 to 63.2%, whereas clinical success rates ranged from 88.3 to 96%.[98-102] Clinical cure and clinical success rates for amoxicillin/clavulanic acid were 58.6 and 87.3%[98] and the rate of clinical success with clarithromycin was 93.3%.[99] In noncomparative trials, bacterial eradication rates were 88.6%[100,101] and 92%.[102] Bacteriological eradication was not examined in the comparative studies. Relapse rates were similar between levofloxacin and amoxicillin/clavulanic acid groups.[98] Relapse rates were 3.7 and 7.9% in 2 noncomparative studies of levofloxacin.[101,102]

3.1.4 Effects on Specific Respiratory Pathogens

In addition to data on clinical response of patients, several controlled clinical trials listed in tables IV to VI examined the ability of levofloxacin to eradicate pathogens cultured before treatment. Bacteriological eradication rates for individual pathogens were not reported in all studies, but results from available data are collated in table VII.

The findings in table VII suggest that, when used to treat infections in adults in clinical practice, levofloxacin has good to excellent efficacy against *S. aureus*, *M. catarrhalis*, *E. coli*, *H. influenzae*, *H. parainfluenzae*, *K. pneumoniae*, *C. pneumoniae*, *M. pneumoniae* and *L. pneumophila* (eradication rates 89.1 to 100%). Eradication rates for levofloxacin against *S. pneumoniae* (89.1%) were similar to the overall rate seen with its comparators (91.0%) amoxicillin/clavulanic acid, cefaclor, and ceftriaxone or cefuroxime axetil (the latter 2 alone or combined). The eradication rate against *P. aeruginosa* (63%) was lower than rates against other pathogens, but was similar to those seen with other comparator agents used against these patho-

Table V. Therapeutic efficacy of oral levofloxacin (LVFX) in adult patients with acute exacerbations of chronic bronchitis

Reference	Study design	Dosage (mg)	Treatment duration (days)	Clinical success rate (%)[a]	Bacteriological eradication rate (%)[b]	Overall efficacy
DeAbate et al.[95]	r, nb, mc, pg, out, PP	LVFX 500 od	5-7	210/222 (94.6)	185/190 (97)	LVFX ≡ CXM
		CXM 250 bid	10	212/229 (92.6)	210/222 (95)	
Habib et al.[96]	r, nb, mc, pg, out, PP	LVFX 500 od	5-7	141/154 (92)	97/103 (94)	LVFX ≡ CEC
		CEC 250 tid	7-10	142/155 (92)	77/89 (87)	
Shah et al.[97]c	r, db, dd; mc, pg, hosp/out, PP	LVFX 250 od	7-10	121/156 (78)	111/144 (77)	LVFX 250 ≡ LVFX 500 ≡ CXM
		LVFX 500 od		108/137 (79)	98/127 (77)	
		CXM 250 bid		88/134 (66)	84/124 (68)	

a Where defined, clinical cure indicated complete resolution of signs and symptoms and clinical success indicated clinical cure plus pronounced improvement, assessed 5-7 days[95,96] or 5-14 days[97] after the end of treatment.

b Bacteriological eradication indicated elimination of pathogenic bacteria at the end of treatment.

c Reported as an abstract.

bid = twice daily; **CEC** = cefaclor; **CXM** = cefuroxime axetil; **db** = double-blind; **dd** = double-dummy; **hosp** = hospitalised patients; **mc** = multicentre; **nb** = nonblind; **od** = once daily; **out** = outpatients; **pg** = parallel group; **PP** = per-protocol efficacy data; **r** = randomised; **tid** = 3 times daily; ≡ indicates equal efficacy between 2 agents.

Table VI. Therapeutic efficacy of oral levofloxacin (LVFX) in adult patients with radiologically confirmed acute maxillary sinusitis

Reference	Study design	Dosage (mg)	Treatment duration (days)	Clinical cure rate (%)[a]	Clinical success rate (%)[a]	Bacteriological eradication rate (%)[b]	Relapse rate (%)[c]	Overall efficacy
Comparative studies								
Adelglass et al.[98]d	r, nb, mc, pg, PP	LVFX 500 od	10-14	156/267 (58.4)	236/267 (88.4)		5/267 (1.8)	LVFX ≡ AMC
		AMC 500/125 tid		157/268 (58.6)	234/268 (87.3)		9/268 (3.4)	
Kahn et al.[99]d	r, nb, mc, pg, PP	LVFX 500 od	14		-[e] (96)			LVFX ≡ CLR
		CLR 500 bid			-[e] (93.3)			
Noncomparative studies								
Gehanno et al.,[100]d data on file[101]	mc	LVFX 500 od	10	151/239 (63.2)		101/117 (88.6)	7/188 (3.7)	
Sydnor et al.[102]	mc	LVFX 500 od	10-14	175/300 (58.3)	265/300 (88.3)	127/138 (92)	21/264 (7.9)	

a Where defined, clinical cure indicated complete resolution of signs and symptoms and clinical success indicated clinical cure plus pronounced improvement.

b Bacteriological eradication indicated elimination of pathogenic bacteria at the end of treatment; rates are based on numbers of patients with pathogenic species after treatment *vs* at pretreatment or on per-pathogen numbers of isolates.

c Relapse was assessed 21 to 28 days post-treatment.

d Reported as an abstract.

e 190 evaluable patients in total.

AMC = amoxicillin/clavulanic acid; **bid** = twice daily; **CLR** = clarithromycin; **mc** = multicentre; **nb** = nonblind; **od** = once daily; **pg** = parallel group; **PP** = per-protocol efficacy data; **r** = randomised; **tid** = 3 times daily; ≡ indicates equal efficacy between 2 agents.

used against these pathogens in the clinical trials.[89,92,95,97] In all, these results should be viewed with some caution because, as is usual with antibacterial trials, only a fraction of total patients had pathogens cultured before treatment and no statistical analysis has been performed on these data.

3.2 Uncomplicated Skin and Soft Tissue Infections

The efficacy of oral levofloxacin 500mg once daily for 7 to 10 days in patients with uncomplicated SSTIs was equivalent to that seen with oral ciprofloxacin 500mg twice daily for 7 to 10 days (table VIII).

In a double-blind study,[104] a 7-day course of levofloxacin was similar in efficacy to a 10-day regimen of ciprofloxacin. Further details about the specific types of infections treated were not available. In 2 trials, 97.8 and 96.1% clinical success rates were observed with levofloxacin, whereas rates with ciprofloxacin were 94.3 and 93.5% (table VIII). Bacteriological eradication rates were 97.5 and 93.2% for levofloxacin and 88.8 and 91.7% with ciprofloxacin. There were no statistically significant differences between the 2 treatments.

3.3 Complicated Urinary Tract Infections Including Acute Pyelonephritis

In patients with complicated UTIs, including acute pyelonephritis, levofloxacin 250 mg/day for 10 days was equivalent in efficacy to ciprofloxacin 250mg twice daily for 10 days or lomefloxacin 400mg once daily for 14 days (table IX).

Clinical cure and clinical success rates were equivalent in patients receiving levofloxacin or its comparators for complicated UTIs or acute pyelonephritis. Clinical cure rates were 84.8 and 82.4% for levofloxacin and lomefloxacin recipients, respectively,[105] but were not assessed in the levofloxacin-ciprofloxacin comparison. Clinical success was seen in 92 and 92.9% of patients receiving levofloxacin in the 2 studies, compared with 88% receiving ciprofloxacin and 88.5% receiving lomefloxacin. Bacteriological eradication rates of 93.6 and 95.3% observed with levofloxacin were similar to the 97.5% with ciprofloxacin and 92.1%

Table VII. Eradication of common respiratory pathogens by levofloxacin (LVFX) in clinical trials. Eradication of bacteria detected using culture or serology before treatment in patients with infections treated with levofloxacin in clinical trials listed in tables IV to VI

Pathogen	LVFX 250-1000 mg/day		References
	eradication rate[a]	percentage eradicated (range[b])	
Gram-positive cocci			
Staphylococcus aureus	99/110	90 (66.7-100)	88,89,92,93,95,96,101,102
Streptococcus pneumoniae	246/276	89.1 (55-100)	88,89,92,93,95-97,101,102
Gram-negative cocci			
Moraxella catarrhalis	132/142	93.0 (82.3-100)	88,89,92,93,95-97,101,102
Gram-negative bacilli			
Escherichia coli	13/13	100 (100)	93,95
Haemophilus influenzae	351/372	94.4 (83.3-100)	88,89,92,93,95-97,101,102
H. parainfluenzae	50/53	94.3 (66.7-100)	88,89,93,95
Klebsiella pneumoniae	13/13	100 (100)	88,93,95
Pseudomonas aeruginosa	31/49	63.3 (43.3-100)	89,92,95,97
'Atypical' pathogens			
Chlamydia pneumoniae[c]	117/122	95.9 (94.5-97.9)	93,94
Mycoplasma pneumoniae[c]	29/29	100 (100)	93,94
Legionella pneumophila[c]	9/10	90 (80-100)	93,94

a Total number of patients in whom pathogens detected before treatment were no longer detected after treatment in all studies/total patients with pathogens detected before treatment in all studies.

b Range of percentages of pathogens eradicated in individual studies.

c Detected using serology or other methods.

with lomefloxacin. Rates of relapse were not reported. In addition, levofloxacin had similar clinical success (93%) and bacteriological eradication (100%) rates to those seen in a combined group (95 and 97.7%, respectively) of ciprofloxacin or lomefloxacin recipients in a subanalysis of 259 patients from these 2 studies who had acute pyelonephritis.[107]

4. Tolerability

4.1 General Tolerability

Levofloxacin is generally well tolerated and most adverse events are transient in duration and mild to moderate in severity. The most common adverse events associated with the use of oral levofloxacin are reported by the manufacturer to be nausea and diarrhoea. With intravenous levofloxacin, phlebitis and reddening of the infusion site may also occur.[108] Collected tolerability data from clinical trials examined in this review (table X) confirm these findings and suggest that adverse events associated with levofloxacin may be dose-related.

Drug-related or possibly drug-related adverse events ranged in incidence from 4 to 4.3% with levofloxacin 250 mg/day, from 5.3 to 26.9% for levofloxacin 500 mg/day and from 22 to 28.8% for levofloxacin 1000 mg/day (table X). The most common adverse events were diarrhoea (1.1 to 2.8%), nausea (1.1 to 3%), abdominal pain (1 to 1.1%), flatulence (1.6%), insomnia (1.1%) and somnolence (2.2%). Changes in liver function tests and thrombocytosis occurred, respectively, in 4.1 and 7.7% of 662 patients with CAP in 2 European clinical trials; such changes have not been reported in other trials. Injection site reactions were reported in 1 to 2.9% of patients receiving levofloxacin intravenously (table X). Levofloxacin therapy was discontinued in 1.8 to 6.5% of patients.

In the comparative studies, levofloxacin was reported to be tolerated as well as cefaclor[96] and ciprofloxacin.[103,104,106,107] In 1 trial it was similar in tolerability to amoxicillin/clavulanic acid,[90] but it was associated with fewer adverse events than amoxicillin/clavulanic acid[98] or lomefloxacin[105] in other studies. The reported incidence of adverse

events with levofloxacin was similar to that of ceftriaxone[92] and cefuroxime axetil[95,97] in some studies, but ceftriaxone and/or cefuroxime axetil appeared to be less well tolerated than levofloxacin in 1 trial.[88,94] The report of a comparison between levofloxacin and clarithromycin provides too few details to assess relative tolerability.[99]

Although the tolerability profile of levofloxacin is generally typical of a fluoroquinolone agent, there appear to be some differences between levofloxacin and other drugs of this class in the overall incidence of adverse events.[109] A review of fluoroquinolone tolerability reported that adverse events occurred in 3.3% of levofloxacin recipients, compared with 4.3% of ofloxacin recipients, 5.5 to 10.2% of ciprofloxacin and 8% of pefloxacin recipients.[109] Withdrawals from clinical trials occurred in 1.3% of patients receiving levofloxacin versus 1.5 to 2.2% of ciprofloxacin, ofloxacin and pefloxacin recipients.[109]

4.2 Serious Adverse Events

With regard to serious adverse events, product labelling for levofloxacin, in common with other fluoroquinolones, urges that patients take care to avoid photosensitisation and discontinue levofloxacin if tendinitis, pseudomembranous colitis or haemolytic reactions (in those with glucose-6-phosphate deficiency) are suspected.[109] During levofloxacin use, tendinitis is rare (<0.1% incidence), pseudomembranous colitis is very rare (<0.01%) and haemolytic reactions occur only in isolated cases.[108]

The safety and efficacy of levofloxacin in patients less than 18 years of age has not been established. However, the ability of levofloxacin to cause osteochondrosis and arthropathy in juvenile animals of several species[75] is similar to that of other fluoroquinolones;[109] as a class, fluoroquinolones are contraindicated for use in children and adolescents for this reason. In the cartilage of juvenile rats[110] or rabbits,[111] oral or intra-articular levofloxacin produced chondrocyte necrosis and erosion with some cavity formation, believed to occur through inhibition of glycosaminoglycan and DNA synthesis and disruption of mitochondrial function. These effects appear to affect both joints and tendons[109] and were similar to those induced by ciprofloxacin.[110]

The phototoxic potential of levofloxacin has been reported to be similar to that of ofloxacin and ciprofloxacin and lower than that of lomefloxacin, enoxacin or nalidixic acid.[1,109] A recent study found no difference in dermal reactions to UVA light or solar simulating radiation between healthy volunteers receiving levofloxacin 500mg once daily for 5 days (n = 24) or those receiving placebo (n = 6).[112]

CNS events may occur in similar or smaller proportions of levofloxacin than ofloxacin recipients.[109] Seizures have been linked to fluoroquinolone overdose or following interaction between fluoroquinolones and theophylline (see section 4.3) or nonsteroidal anti-inflammatory drugs (NSAIDs).[109] However, seizures have been reported only rarely with levofloxacin (<0.1%),[108] and may be less

Table VIII. Therapeutic efficacy of oral levofloxacin (LVFX) in adult patients with uncomplicated skin and soft tissue infections

Reference	Study design	Dosage (mg)	Treatment duration (days)	Clinical success rate (%)[a]	Bacteriological eradication rate (%)[b]	Overall efficacy
Nichols et al.[103]	r, nb, mc, pg, PP	LVFX 500 od	7-10	178/182 (97.8)	153/157 (97.5)	LVFX ≡ CIP
		CIP 500 bid		182/193 (94.3)	135/152 (88.8)	
Nicodemo et al.[104]	r, db, mc, pg, PP	LVFX 500 od	7	124/129 (96.1)	97/103d (93.2)	LVFX ≡ CIP
		CIP 500 bid	10	116/124 (93.5)	93/101 (91.7)	

a Where defined, clinical cure indicated complete resolution of signs and symptoms and clinical success indicated clinical cure plus pronounced improvement, assessed 1 to 10 days after treatment[104] or 2 to 7 days after treatment.[103]

b Bacteriological eradication indicated elimination of pathogenic bacteria at the end of treatment.

bid = twice daily; **CIP** = ciprofloxacin; **db** = double-blind; **mc** = multicentre; **nb** = nonblind; **NS** = not stated; **od** = once daily; **pg** = parallel group; **PP** = per-protocol efficacy data; **r** = randomised; ≡ indicates equal efficacy between 2 agents.

Table IX. Therapeutic efficacy of oral levofloxacin (LVFX) in adult patients with complicated urinary tract infections or acute pyelonephritis

Reference	Study design	Dosage (mg)	Clinical cure rate (%)[a]	Clinical success rate (%)[a]	Bacteriological eradication rate (%)[b]	Overall efficacy
Klimberg et al.[105]	r, nb, mc, pg, PP	LVFX 250 od × 10 days	145/171 (84.8)	159/171 (92.9)	168/176 (95.3)	LVFX ≡ LOM
		LOM 400 od × 14 days	136/165 (82.4)	146/165 (88.5)	152/165 (92.1)	
Richard et al.[106]c	r, db, mc, pg, PP	LVFX 250 od × 10 days		116/126 (92)	88/94[d] (93.6)	LVFX ≡ CIP
		CIP 250 bid × 10 days		99/113 (88)	77/79[d] (97.5)	

a Where defined, clinical cure indicated complete resolution of signs and symptoms and clinical success indicated clinical cure plus pronounced improvement, assessed 5-9 days after treatment[105] or at an undefined time after treatment.[106]

b Bacteriological eradication indicated elimination of pathogenic bacteria at the end of treatment; rates are based on numbers of patients with pathogenic species after treatment *vs* at pretreatment or on per-pathogen numbers of isolates.

c Reported as an abstract.

bid = twice daily; **CIP** = ciprofloxacin; **db** = double-blind; **LOM** = lomefloxacin; **mc** = multicentre; **nb** = nonblind; **od** = once daily; **pg** = parallel group; **PP** = per-protocol efficacy data; **r** = randomised; ≡ indicates equal efficacy between the 2 agents.

common with levofloxacin than with some other fluoroquinolones. In mice, a higher dosage of levofloxacin than ofloxacin or its *R*(+)-isomer was required to induce death by convulsion.[113] In addition, the convulsive effects of levofloxacin and ofloxacin were enhanced only by ketoprofen, whereas enoxacin or ciprofloxacin could also be enhanced by ibuprofen, loxoprofen or oxaprozin.[113] Although hallucinations and psychoses have been reported to occur in 0.02 to 0.06% of patients receiving ofloxacin,[109] visual and auditory disturbances and hallucinations have been reported in <0.01% of levofloxacin recipients.[108]

4.3 Drug Interactions

Levofloxacin, like other fluoroquinolone agents, may interact with divalent or trivalent cations, leading to reduced absorption of levofloxacin. Magnesium- or aluminium-containing antacids or ferrous salts may chelate with levofloxacin.[114-117] The extent of adsorption of levofloxacin (48.1%) onto aluminium hydroxide *in vitro* was similar to that of ofloxacin (47.2%) and less than that of enoxacin (61%) or norfloxacin (72%).[115] In healthy volunteers, the AUC of levofloxacin 200mg was reduced by aluminium hydroxide gel 1000mg (from 9.29 to 5.11 mg/L · h), but this decrease was less than that seen with ciprofloxacin 200mg (AUC reduced from 6.35 to 0.76 mg/L · h).[114] Thus, levofloxacin may be less prone to chelation than other fluoroquinolones. Chelation is not seen between levofloxacin and calcium carbonate,[116] and although levofloxacin may adsorb to sucralfate, this interaction does not occur if the 2 agents are administered ≥2 hours apart.[72]

The potential for levofloxacin to interact with NSAIDs, theophylline or antihyperglycaemic drugs is assumed on the basis of interactions between these agents and other fluoroquinolones. Levofloxacin had only minor effects on theophylline pharmacokinetics in healthy volunteers.[118,119] In 7 healthy volunteers receiving theophylline 400 mg/day for 9 days plus levofloxacin 300 mg/day on days 5 to 9, the ratio of day 7 to day 4 theophylline AUC and C_{max} values were 1.11 and 1.09.[118] When a theophylline 4.5 mg/kg intravenous infusion was administered to 14 healthy volunteers after 9 doses of placebo or levofloxacin 500mg every 12 hours, theophylline C_{max}, AUC and half-life values were unchanged.[119] However, increases in the half-life and plasma levels of theophylline have been observed in patients taking other fluoroquinolones.[75] The interaction between the combination may result in an increased risk of seizures (section 4.3) or other adverse events.[75] Similarly, concomitant use of fluoroquinolones with NSAIDs may increase the potential for seizures.[75] Fenbufen has been shown to increase levofloxacin concentrations (by 13%).[108] Fluoroquinolones may also increase the risk of hyper- or hypoglycaemia when administered concurrently with antihyperglycaemic drugs,[75] although there are no publish-

Table X. Adverse events associated with intravenous or oral levofloxacin (LVFX): drug-related or possibly drug-related events reported in clinical trials of 5- to 14-day therapy in ≈2900 patients with respiratory tract, urinary tract or skin and soft tissue infections enrolled in clinical trials[90,92-96,98,101,102,104-106]

Adverse event	Patients with event/total patients (%)		
	LVFX 250 mg/day	LVFX 500 mg/day	LVFX 1000 mg/day
Total patients with drug-related adverse events	NS[a] (4)[106] 10/232 (4.3)[105]	14/263 (5.3)[93] 17/291 (5.8)[94] 13/186 (7)[96] NS[b] (7.4)[98] 29/329 (8.8)[102] 12/135 (8.9)[104] 24/243 (10)[95] 33/239 (13.8)[101] 46/171 (26.9)[90]	68/314 (22)[92] 51/177 (28.8)[90]
Diarrhoea		2/186 (1.1)[96] NS[b] (1.3)[98] 4/291 (1.4)[94] 2/135 (1.5)[104] 4/263 (1.5)[93] 4/243 (1.6)[95]	6/314 (1.9)[92] 5/177 (2.8)[90]
Nausea		3/263 (1.1)[93] 5/291 (1.7)[94] NS[b] (1.7)[98] 4/186 (2.1)[96] 6/243 (2.5)[95] 4/135 (3)[104]	
Abnormal liver function tests		5/171 (2.9)[90]	6/177 (3.4)[90] 16/314 (5.1)[92]
Abdominal pain		NS[b] (1)[98] 2/186 (1.1)[96]	
Flatulence		3/186 (1.6)[96]	
Vaginitis		NS[b] (1.1)[98] 5/243 (2.1)[95]	
Thrombocytosis		18/171 (10.5)[90]	10/314 (3.2)[92] 23/177 (13)[90]
Nervous system			6/314 (1.9)[92]
Insomnia		2/186 (1.1)[96]	
Somnolence		3/135 (2.2)[104]	
Injection site reactions		3/291 (1)[94]	9/314 (2.9)[92]
Discontinuation due to adverse events	8/232 (3.4)[105]	6/329 (1.8)[101] 5/171 (2.9)[90] 7/243 (2.9)[95] 9/263 (3.4)[93] 13/291 (4.4)[94] 11/239 (4.6)[101] 7/135 (5.2)[104] 12/186 (6.5)[95]	8/177 (4.5)[90] 15/314 (4.8)[92]

a Study arm contained >126 patients.

b Study arm contained >267 patients.

NS = not stated.

ed data suggesting that this interaction occurs with levofloxacin.

Interactions with some other agents have been characterised and are known to be minor or non-existent. Although levofloxacin absorption is not affected by concurrent ranitidine,[116,117] cimetidine[120] or probenecid,[120] both cimetidine and probenecid inhibit tubular secretion of levoflox-

acin.[120] The clinical significance of this interaction is uncertain. The pharmacokinetics or pharmacodynamics of warfarin do not appear to be affected by levofloxacin,[121] but pharmacodynamic monitoring of warfarin effects should be undertaken when drugs are added to a warfarin regimen. Levofloxacin and zidovudine also do not appear to interact with each other pharmacokinetically.[122] Dosage adjustments do not appear to be warranted when levofloxacin is administered concurrently with either cyclosporin[123] or digoxin.[75]

5. Dosage and Administration

5.1 Indications and Dosage Recommendations

Levofloxacin is indicated in the US for oral or intravenous administration to adults with mild-to-moderate acute sinusitis, AECB, CAP, complicated UTIs including pyelonephritis, and SSTIs.[75] In Europe, levofloxacin may be administered orally to adults with mild-to-moderate acute sinusitis, AECB, CAP, complicated UTIs including pyelonephritis, and SSTIs or intravenously to adult patients with CAP, complicated UTIs including pyelonephritis and SSTIs.[108] Specific dosage recommendations also differ between these geographical areas (table XI). Higher levofloxacin dosages may be used to treat CAP in Europe (up to 500mg twice daily) than in the US (maximum 500mg once daily), lower dosages may be used to treat AECB in Europe (250 or 500mg once daily *vs* 500mg once daily in the US), and both higher and lower dosages may be used to treat SSTIs in Europe (250, 500 or 1000 mg/day *vs* 500 mg/day).

Levofloxacin is indicated for mild, moderate and severe CAP. As may occur with other drugs in this class, some strains of *P. aeruginosa* may develop resistance fairly rapidly during treatment with levofloxacin.[75]

When administered intravenously, levofloxacin injection should be given by slow (60-minute) intravenous infusion.[75] Oral levofloxacin may be taken without regard to meals. With either dosage form, patients should be advised to drink fluids liberally.[75]

Table XI. Dosage recommendations for the use of levofloxacin in patients in the US[75] and Europe[108]

Indication	Oral dosage (mg)	Intravenous dosage (mg)[a]	Duration (days)
US recommendations			
Acute sinusitis	500 od	500 od	10-14
AECB	500 od	500 od	7
CAP	500 od	500 od	7-14
Complicated UTIs or pyelonephritis	250 od	250 od	10
Uncomplicated SSTIs	500 od	500 od	7-10
European recommendations			
Acute sinusitis	500 od		10-14
AECB	250-500 od		7-10
CAP	500 od or bid	500 od or bid	7-14
Complicated UTIs or pyelonephritis	250 od	250 od[b]	7-10
SSTIs	250 od or 500 od or bid	500 bid	7-14

a Treatment should be continued for 48 to 72 hours after evidence of bacterial eradication has been obtained or the patient has become afebrile. Depending on the condition of the patient, a move from intravenous to oral levofloxacin may be made after a few days.

b Consider raising the dose in cases of severe infection.

AECB = acute exacerbations of chronic bronchitis; **bid** = twice daily; **CAP** = community-acquired pneumonia; **od** = once daily; **SSTIs** = skin or soft tissue infections; **UTIs** = urinary tract infections.

5.2 Drug Interactions

To prevent a reduction in levofloxacin absorption, preparations containing di- or trivalent cations (e.g. iron salts, magnesium- or aluminium-containing antacids, but not calcium carbonate) should be taken 2 hours before or after levofloxacin, and sucralfate should be taken 2 hours after levofloxacin. Although levofloxacin and theophylline do not appear to interact pharmacokinetically (section 4.3), seizure threshold may be lowered when the two are administered concurrently. The same applies for NSAIDs or other agents that lower seizure thresholds. Levofloxacin combined with either probenecid or cimetidine should be used with caution in patients with renal impairment.[108]

5.3 Use in Special Populations

The safety and efficacy of levofloxacin in children and adolescents below the age of 18 years has not been established. Fluoroquinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species.[75]

Levofloxacin should not be used in patients with epilepsy or a history of tendon disorders related to fluoroquinolone use, or during pregnancy or breastfeeding.[108]

In patients with impaired renal clearance (creatinine clearance <3 L/h or <50 ml/min), dosages of levofloxacin should be adjusted on the basis of creatinine clearance. Specific recommendations for dosage adjustments vary in different countries. Local prescribing information should be consulted.

No additional doses are required after haemodialysis or continuous ambulatory peritoneal dialysis. No dosage adjustment is necessary when levofloxacin is used in patients with liver impairment or in the elderly (except that necessitated by impaired renal function).[108]

6. Place of Levofloxacin in the Management of Infectious Diseases

Choices of antibacterial agents and preferred methods for their use vary internationally and regionally. Nonetheless, there are major factors that affect this choice everywhere. Chief among them is whether a drug works as well as other available agents against key pathogens; regional susceptibility patterns are an important consideration in this respect. Next, does the drug possess properties that allow it to be effective at the sites of infection? Can it be administered easily to patients and is it well tolerated? What factors limit its use? How does its cost compare with that of other therapies?

For the treatment of respiratory tract infections, established fluoroquinolone agents (such as ciprofloxacin and ofloxacin) possess excellent activity against the major Gram-negative pathogens but have variable and low activity against *S. pneumoniae*. For this reason, these fluoroquinolones are currently not recommended as first-line therapy for respiratory tract infections.[124] However, many of the newer fluoroquinolone agents possess enhanced activity against streptococci and so offer a new therapeutic option in the treatment of respiratory tract infections. Thus, levofloxacin and other newer fluoroquinolones are now recommended as first-line therapy for CAP and other respiratory tract infections caused by *S. pneumoniae*, *H. influenzae*, *Legionella* spp., *M. pneumoniae* and *C. pneumoniae*.[125]

In particular, median MIC_{90} values for levofloxacin against *S. pneumoniae* (fig. 1a), regardless of the penicillin sensitivity of this bacterium, are 1 mg/L, i.e. 2-fold lower than those of both ofloxacin and ciprofloxacin. Although this is not a 2-dilution difference between agents, all MIC_{90} values were well within the NCCLS breakpoint for susceptibility of this organism to levofloxacin, unlike with ofloxacin (all are at or above the breakpoint) or ciprofloxacin (for which no breakpoint exists).[51] The clinical significance of these differences is difficult to gauge; however, levofloxacin demonstrated good activity against *S. pneumoniae* in clinical trials with an overall eradication rate of 89% (range 55 to 100%, table VII). On the other hand, sparfloxacin appears to be 4-fold and trovafloxacin 8-fold more active than levofloxacin against this pathogen (fig. 1a). Susceptibility breakpoints for the newer fluoroquinolones sparfloxacin and trovafloxacin have not been defined and much less information is available about their activity and tolerability.

Predictably, levofloxacin consistently achieved eradication rates of >90% for other respiratory pathogens, including atypical agents (table VII). In comparative clinical trials, levofloxacin achieved efficacy rates similar to those of several β-lactam agents (amoxicillin/clavulanic acid, ceftriaxone, cefuroxime axetil and cefaclor) in the treatment of lower respiratory tract infections, and amoxicillin and clarithromycin in acute maxillary sinusitis. No clinical comparisons between levofloxacin and the other newer fluoroquinolone agents have yet been performed in these indications. In keeping with its *in vitro* activity profile, and in common with other

fluoroquinolone agents, a lower eradication rate was evident against *P. aeruginosa* (63%; table VII). Surveillance of resistance to the fluoroquinolones should therefore be encouraged, especially if these agents are to be used more widely in the community.

Another important aspect of the clinical profile of levofloxacin is the degree of experience with regard to tolerability of the agent. An overview of trials,[109] suggests that levofloxacin (3.3%) may be associated with fewer drug-related adverse events than either ciprofloxacin (5.5 to 10.2%) or ofloxacin (4.3%), and that some drug interactions may be less common with levofloxacin than other fluoroquinolones (section 4.3). Levofloxacin differs from the newer agents in having been well tested and appears to be at least as well tolerated as the older, established fluoroquinolones such as ciprofloxacin and ofloxacin, while also appearing to have fewer significant drug interactions. It remains to be seen whether the newer agents will in time match this claim. Until they can, for the treatment of respiratory tract infections, levofloxacin appears to be a better option. In addition, levofloxacin has the advantage of being 100% orally available, such that it can be used sequentially as intravenous followed by oral administration without any adjustment in dosage. Levofloxacin also may be administered in once-daily regimens, which may aid compliance.

The efficacy of levofloxacin in the treatment of complicated UTIs, including acute pyelonephritis, makes it a clear alternative to other fluoroquinolones in these infections. Fluoroquinolones also may be good choices for use in the treatment of SSTIs because of their wide distribution to the sites of infection (table III).[126] When a fluoroquinolone is indicated for use in uncomplicated SSTIs, levofloxacin appears to be a good alternative.

In conclusion, levofloxacin can be administered in a once-daily regimen for the treatment of AECB, CAP, acute maxillary sinusitis, complicated urinary tract infections including pyelonephritis and uncomplicated SSTIs. Levofloxacin is distinguished by a well-characterised tolerability profile and enhanced activity against *S. pneumoniae* compared with ciprofloxacin or ofloxacin. Clinicians should consider the relative merits of improved activity against *S. pneumoniae* versus a known tolerability profile when choosing between levofloxacin and other newer fluoroquinolone agents for the treatment of respiratory tract infections.

References

1. Davis R, Bryson HM. Levofloxacin: a review of its antibacterial activity, pharmacokinetics and therapeutic efficacy. Drugs 1994 Apr; 47: 677-700
2. Hammerschlag MR, Qumei KK, Roblin PM. *In vitro* activities of azithromycin, clarithromycin, L-ofloxacin, and other antibiotics against *Chlamydia pneumoniae*. Antimicrob Agents Chemother 1992; 36 (7): 1573-4
3. Bauernfeind A. Comparison of the antibacterial activities of the quinolones Bay 12-8039, gatifloxacin (AM 1155), trovafloxacin, clinafloxacin, levofloxacin and ciprofloxacin. J Antimicrob Chemother 1997; 40: 639-51
4. Biedenbach DJ, Jones RN. In vitro evaluation of DV-7751a, a new fluoroquinolone with an enhanced spectrum of activity against Gram-positive aerobic organisms and anaerobes. Antimicrob Agents Chemother 1995 Jul; 39: 1636-43
5. von Eiff C, Peters G. *In vitro* activity of ofloxacin, levofloxacin and D-ofloxacin against staphylococci. J Antimicrob Chemother 1996 Aug; 38: 259-63
6. Child J, Andrews J, Boswell F, et al. The *in vitro* activity of CP 99,219, a new naphthyridone antimicrobial agent: a comparison with fluoroquinolone agents. J Antimicrob Chemother 1995 Jun; 35: 869-76
7. Miyazaki S, Domon H, Tateda K, et al. In vitro and in vivo antibacterial activities of CS-940, a new fluoroquinolone, against isolates from patients with respiratory infections. Antimicrob Agents Chemother 1997 Nov; 41: 2582-5
8. Goldstein EJC, Citron DM, Hunt Gerardo S, et al. Comparative in vitro activities of DU-6859a, levofloxacin, ofloxacin, sparfloxacin, and ciprofloxacin against 387 aerobic and anaerobic bite wound isolates. Antimicrob Agents Chemother 1997 May; 41: 1193-5
9. Goldstein EJC, Nesbit CA, Citron DM. Comparative *in vitro* activities of azithromycin, Bay y 3118, levofloxacin, sparfloxacin, and 11 other oral antimicrobial agents against 194 aerobics and anaerobic bite wound isolates. Antimicrob Agents Chemother 1995 May; 39: 1097-100
10. Fuchs PC, Barry AL, Brown SD. Prevalence of resistance to three fluoroquinolones: assessment of levofloxacin disk test error rates and surrogate predictors of levofloxacin susceptibility. Antimicrob Agents Chemother 1996 Jul; 40: 1633-9
11. Eliopoulos GM, Wennersten CB, Moellering Jr RC. Comparative *in vitro* activity of levofloxacin and ofloxacin against Gram-positive bacteria. Diagn Microbiol Infect Dis 1996 May; 25: 35-41
12. Cooper I, Isbell DJ, Kruszynski JA. Comparative *in vitro* activity of L-ofloxacin and FK037 to other agents against 10,040 fresh clinical isolates. Int J Antimicrob Agents 1996; 6 (4): 201-21
13. Rolston KVI, Ho DH, LeBlanc B, et al. *In vitro* activity of trovafloxacin against clinical bacterial isolates from patients

with cancer. J Antimicrob Chemother 1997 Jun; 39 Suppl. B: 15-22
14. Takahashi Y, Masuda N, Otsuki M, et al. *In vitro* activity of HSR-903, a new quinolone. Antimicrob Agents Chemother 1997 Jun; 41: 1326-30
15. Hoogkamp-Korstanje JAA. *In vitro* activities of ciprofloxacin, levofloxacin, lomefloxacin, ofloxacin, pefloxacin, sparfloxacin and trovafloxacin against Gram-positive and Gram-negative pathogens from respiratory tract infections. J Antimicrob Chemother 1997 Sep; 40: 427-31
16. Yamane N, Jones RN, Frei R, et al. Levofloxacin *in vitro* activity: results from an international study with ofloxacin and ciprofloxacin. J Chemother 1994 Apr; 6: 83-91
17. Casellas JM, Gilardoni M, Tomè G, et al. Comparative *in vitro* activity of levofloxacin against isolates from adult patients with community-acquired lower respiratory tract infections [abstract no. P1148]. 8th European Congress of Clinical Microbiology and Infectious Diseases. Lausanne; 1997 May 25-8
18. Felmingham D, Robbins M, Mathias I, et al. A European multicentre study of the comparative *in vitro* susceptibility of Gram-positive bacteria to levofloxacin [abstract no. P018]. 20th International Congress of Chemotherapy; 1997 Jun 29; 94
19. Giamarellos-Bourboulis EJ, Grecka P, Galani I. Comparative *in vitro* activity and killing effect of trovafloxacin, DU-6859a, levofloxacin and sparfloxacin against *Staphylococcus aureus*: focus on methicillin-resistant isolates. Clin Drug Invest 1997 Oct; 14: 330-6
20. Hamilton-Miller JMT, Shah S. Activities of ciprofloxacin, levofloxacin, ofloxacin and sparfloxacin against speciated coagulase-negative staphylococci sensitive and resistant to fluoroquinolones. Int J Antimicrob Agents 1997; 9 (2): 127-30
21. Brueggemann AB, Kugler KC, Doern GV. *In vitro* activity of BAY 12-8039, a novel 8-methoxyquinolone, compared to activities of six fluoroquinolones against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Antimicrob Agents Chemother 1997 Jul; 41: 1594-7
22. Klugman KP, Capper T, Bryskier A. In vitro susceptibility of penicillin-resistant *Streptococcus pneumoniae* to levofloxacin, selection of resistant mutants, and time-kill synergy studies of levofloxacin combined with vancomycin, teicoplanin, fusidic acid, and rifampin. Antimicrob Agents Chemother 1996 Dec; 40: 2802-4
23. Hunt Gerardo S, Citron DM, Claros MC, et al. Comparison of Etest to broth microdilution method for testing *Streptococcus pneumoniae* susceptibility to levofloxacin and three macrolides. Antimicrob Agents Chemother 1996 Oct; 40: 2413-5
24. Fremaux A, Sissla G, Geslin P. *In vitro* bacteriostatic activity of levofloxacin and three other fluoroquinolones against penicillin-susceptible and penicillin-resistant *Streptococcus pneumoniae* [abstract no. P1147]. 8th European Congress of Clinical Microbiology and Infectious Diseases, Lausanne, Switzerland. 1997 May 25-8
25. Reinert R, Lütticken R, Lemperle M, et al. Comparative *in vitro* activity of ofloxacin, levofloxacin, D (-)ofloxacin, ciprofloxacin, amoxicillin, cefpodoxime, cefixime, cefuroxime, faropenem, erythromycin and tetracycline against *S. pneumoniae* [abstract]. 20th International Congress of Chemotherapy; 1997 Jun 29; 92-3
26. Tomizawa H, Tateda K, Miyazaki S, et al. Antibacterial activity of AM-1155 against penicillin-resistant *Streptococcus pneumoniae*. J Antimicrob Chemother 1998; 41: 103-6
27. Pfaller MA, Jones RN. Comparative antistreptococcal activity of two newer fluoroquinolones, levofloxacin and sparfloxacin. Diagn Microbiol Infect Dis 1997; 29: 199-201
28. Barry AL, Fuchs PC, Allen SD, et al. *In vitro* susceptibility of *Streptococcus pneumoniae* to the d- and l-isomers of ofloxacin: interpretive criteria and quality control limits. J Antimicrob Chemother 1996 Feb; 37: 365-9
29. Biedenbach DJ, Jones RN. The comparative antimicrobial activity of levofloxacin tested against 350 clinical isolates of streptococci. Diagn Microbiol Infect Dis 1996 May; 25: 47-51
30. Pankuch GA, Jacobs MR, Appelbaum PC. Activity of CP 99,219 compared with DU-6859a, ciprofloxacin, ofloxacin, levofloxacin, lomefloxacin, tosufloxacin, sparfloxacin and grepafloxacin against penicillin-susceptible and -resistant pneumococci. J Antimicrob Chemother 1995 Jan; 35: 230-2
31. Giron KP, Gross ME, Musher DM, et al. *In vitro* antimicrobial effect against *Streptococcus pneumoniae* of adding rifampin to penicillin, ceftriaxone, or l-ofloxacin. Antimicrob Agents Chemother 1995 Dec; 39: 2798-800
32. Georgopoulos A, Moser C, Buxbaum A, et al. Antipneumococcal activity of Bay 12-8039 and trovofloxacin in comparison to older quinolones [abstract]. 20th International Congress of Chemotherapy; 1997 Jun 29; 80
33. Cormican MG, Runyon BA, Jones RN. *In vitro* activity of levofloxacin and FK-037 against aerobic isolates from spontaneous bacterial peritonitis. J Chemother 1995 Jun; 7: 197-200
34. Visalli MA, Jacobs MR, Appelbaum PC. Susceptibility of twenty penicillin-susceptible and -resistant pneumococci to levofloxacin, ciprofloxacin, ofloxacin, erythromycin, azithromycin, and clarithromycin by MIC and time-kill. Diagn Microbiol Infect Dis 1997 Jul; 28: 131-7
35. Keller N, Smollen G, Davidson Y, et al. The sensitivity of *Streptococcus pneumoniae* to levofloxacin and other antibiotic drugs [abstract no. P018]. 20th International Congress of Chemotherapy; 1997 Jun 29; 94
36. Thomson K, Chartrand S, Sanders C, et al. Activity of levofloxacin and 12 comparison agents against pediatric isolates of Streptococcus pneumoniae with varying levels of penicillin resistance [abstract]. 20th International Congress of Chemotherapy 1997 Jun 29: 92
37. Hayden MK, Matushek MG, Trenholme GM. Comparison of the *in vitro* activity of levofloxacin and other antimicrobial agents against vancomycin-susceptible and vancomycin-resistant *Enterococcus species*. Diagn Microbiol Infect Dis 1995 Aug; 22: 349-52
38. Soussy CJ, Cluzel M, Ploy MC, et al. *In vitro* antibacterial activity of a new fluoroquinolone, levofloxacin, against hospital isolates: a multicentre study [abstract no. P405]. 8th European Congress of Clinical Microbiology and Infectious Diseases. Lausanne, Switzerland. May 25-8, 1997
39. Dholakia N, Rolston KVI, Ho DH, et al. Susceptibilities of bacterial isolates from patients with cancer to levofloxacin and other quinolones. Antimicrob Agents Chemother 1994 Apr; 38: 848-52
40. Felmingham D, Robbin MJ, Mathias I, et al. Results of a European multicentre study of the comparative *in vitro* susceptibility of Gram-negative bacteria to levofloxacin [abstract no. P1150]. 8th European Congress of Clinical Microbiology and Infectious Diseases. Lausanne; 1997 May 25-8
41. Visalli MA, Bajaksouzian S, Jacobs MR, et al. Comparative activity of trovafloxacin, alone and in combination with other agents, against gram-negative nonfermentative rods. Antimicrob Agents Chemother 1997 Jul; 41: 1475-81
42. Flynn CM, Johnson DM, Jones RN. *In vitro* efficacy of levofloxacin alone or in combination tested against multi-resistant *Pseudomonas aeruginosa* strains. J Chemother 1996 Dec; 8: 411-5

43. Visalli M, Bajaksouzian S, Jacobs M, et al. Synergy between levofloxacin and 4 drugs against *Pseudomonas aeruginosa* [abstract no. E145]. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy 1997 Sep 28: 140
44. Visalli M, Spangler SK, Jacobs M, et al. Activity of levofloxacin compared to 9 drugs against non-fermenters [abstract no. P018]. 20th International Congress of Chemotherapy; Sydney; 1997 Jun 29-Jul 3
45. Kitzis MD, Goldstein FW, Miegi M, et al. *In vitro* activity of levofloxacin, a new fluoroquinolone: evaluation on *H. influenzae* and *M. catarrhalis* [abstract no. P408]. 8th European Congress of Clinical Microbiology and Infectious Diseases. Lausanne; 1997 May 25-8
46. Baltch AL, Smith RP, Ritz W. Inhibitory and bactericidal activities of levofloxacin, ofloxacin, erythromycin, and rifampicin used singly and in combination against *Legionella pneumophila*. Antimicrob Agents Chemother 1995 Aug; 39: 1661-6
47. Edelstein PH, Edelstein MAC, Lehr KH. *In vitro* activity of levofloxacin against clinical isolates of *Legionella* spp, its pharmacokinetics in guinea pigs, and use in experimental *Legionella pneumophila* pneumonia. J Antimicrob Chemother 1996 Jan; 37: 117-26
48. MacGowan AP, Bowker KE, Wootton M, et al. *In vitro* activities of Y-688, a new 7-substituted fluoroquinolone, against anaerobic bacteria. Antimicrob Agents Chemother 1998; 42 (2): 419-24
49. Kaku M, Ishida K, Irifune K, et al. *In vitro* and *in vivo* activities of sparfloxacin against *Mycoplasma pneumoniae*. Antimicrob Agents Chemother 1994 Apr; 38: 738-41
50. Martin SJ, Pendland SL, Chen C. In vitro synergy testing of macrolide-quinolone combinations against 41 clinical isolates of *Legionella*. Antimicrob Agents Chemother 1996 Jun; 40: 1419-21
51. NCCLS. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically - 4h ed; Approved Standard. NCCLS Document M7-A4 (ISBN 1-56238-309-4). NCCLS, 940 West Valley Road, Suite 1400, Wayne Pennsylvania, 19087, USA
52. Takahashi H, Kikuchi T, Shoji S, et al. Characterization of *gyrA, gyrB, glrA* and *glrB* mutations in fluoroquinolone-resistant clinical isolates of *Staphylococcus aureus*. J Antimicrob Chemother 1998; 41: 49-57
53. Kitzis MD, Goldstein FW, Acar JF. Selection of one step resistant mutants of *S. pneumoniae* (SP) by levofloxacin comparatively to other fluoroquinolones (FQ) [abstract]. 35th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1995 Sep 17; 62
54. Sulavik M, Peshick S, Barg N. Ciprofloxacin (CIP) selects low-level quinolone-resistant mutants (LLQR) of meth-resistant (MR) and -susceptible (MS) *Staphylococcus aureus* (SA) more frequently than ofloxacin (OFX) or levofloxacin (LFX) *in vitro* and *in vivo* [abstract]. 36th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1996 Sep 15; 54
55. Entenza JM, Vouillamoz J, Glauser MP, et al. Levofloxacin versus ciprofloxacin, flucloxacillin, or vancomycin for treatment of experimental endocarditis due to methicillin-susceptible or -resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 1997 Aug; 41: 1662-7
56. Evans ME, Titlow WB. Levofloxacin selects fluoroquinolone-resistant methicillin-resistant *Staphylococcus aureus* less frequently than ciprofloxacin. J Antimicrob Chemother 1998; 41: 285-8
57. Thornsberry C, Ogilvie P, Kahn J, et al. Surveillance of antimicrobial resistance in *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis* in the United States in 1996-1997 respiratory season. Diagn Microbiol Infect Dis 1997; 29: 249-57
58. Zeller V, Fourgeaud M, Moreau NJ. Accumulation of fluoroquinolones by *Streptococcus pneumoniae* and resistance arising from active fluoroquinolone efflux [abstract no. C57]. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy; Toronto; 1997 Sep 28-Oct 1
59. Itokazu GS, Quinn JP, Bell-Dixon C, et al. Antimicrobial resistance rates among aerobic Gram-negative bacilli recovered from patients in intensive care units: evaluation of a national postmarketing surveillance program. Clin Infect Dis 1996; 23: 779-84
60. Raddatz JK, Ostergaard BE, Hovde LB, et al. An *in vitro* pharmacodynamic (PD) evaluation of levofloxacin (L) against a TEM-10 producing *Klebsiella pneumoniae* (KP) isolate and two strains of *Pseudomonas aeruginosa* (PA) [abstract]. 36th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1996 Sep 15; 13
61. Markus A, Isert D, Klesel N, et al. Killing activity of levofloxacin (LEF) and ciprofloxacin (CIP) against *Streptococcus pneumoniae in vitro* and *in vivo* [abstract]. 35th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1995 Sep 17; 90
62. Odenholt I, Löwdin E, Cars O. Killing effect of levofloxacin compared to that of ciprofloxacin and sparfloxacin [abstract]. 36th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1996 Sep 15; 82
63. Fuchs PC, Barry AL, Brown SD. *Streptococcus pneumoniae* killing rate and post-antibiotic effect of levofloxacin and ciprofloxacin. J Chemother 1997; 9 (6): 391-3
64. Spangler SK, Jacobs MR, Appelbaum PC. Bactericidal activity of DU-6859a compared to activities of three quinolones, three β-lactams, clindamycin, and metronidazole against anaerobes as determined by time-kill methodology. Antimicrob Agents Chemother 1997 Apr; 41: 847-9
65. George J, Morrissey I. The bactericidal activity of levofloxacin compared with ofloxacin, D-ofloxacin, ciprofloxacin, sparfloxacin and cefotaxime against *Streptococcus pneumoniae*. J Antimicrob Chemother 1997 Jun; 39: 719-23
66. Pendland SL, Danziger LH. The postantibiotic effect of levofloxacin on *Bacteroides* species [abstract]. Clin Infect Dis 1995 Sep; 21: 748
67. Licata L, Smith CE, Goldschmidt RM, et al. Comparison of the postantibiotic and postantibiotic sub-MIC effects of levofloxacin and ciprofloxacin on *Staphylococcus aureus* and *Streptococcus pneumoniae*. Antimicrob Agents Chemother 1997 May; 41: 950-5
68. Fu KP, Foleno B, Rosenthale ME. The postantibiotic suppressive effect of L-ofloxacin, an optically active isomer of ofloxacin. Diagn Microbiol Infect Dis 1992; 15: 375-8
69. Spangler SK, Lin G, Jacobs MR, et al. Postantibiotic effect and postantibiotic sub-MIC effect of levofloxacin compared to those of ofloxacin, ciprofloxacin, erythromycin, azithromycin and clarithromycin against 20 pneumococci. Antimicrob Agents Chemother 1998 May; 42 (5): 1253-5
70. Smith RP, Baltch AL, Franke M, et al. Effect of levofloxacin, erythromycin or rifampicin pretreatment on growth of *Legionella pneumophila* in human monocytes. J Antimicrob Chemother 1997 Nov; 40: 673-8
71. Fish DM, Chow AT. The clinical pharmacokinetics of levofloxacin. Clin Pharmacokinet 1997 Feb; 32: 101-19
72. Lee L-J, Hafkin B, Lee I-D, et al. Effects of food and sucralfate on a single oral dose of 500 milligrams of levofloxacin in

healthy subjects. Antimicrob Agents Chemother 1997 Oct; 41: 2196-200
73. Chien S-C, Rogge MC, Gisclon LG, et al. Pharmacokinetic profile of levofloxacin following once-daily 500-milligram oral or intravenous doses. Antimicrob Agents Chemother 1997 Oct; 41: 2256-60
74. Chien S-C, Wong FA, Fowler CL, et al. Double-blind evaluation of the safety and pharmacokinetics of multiple oral once-daily 750-milligram and 1-gram doses of levofloxacin in healthy volunteers. Antimicrob Agents Chemother 1998 Apr; 42 (4): 885-8
75. Ortho Pharmaceutical Corporation and McNeil Pharmaceutical. Once-a-day LevaquinTM (levofloxacin) tablets/injection. Product information. Raritan, NJ, USA 09969-0602
76. Ortho-McNeil Pharmaceuticals. 1998 Data on file. Raritan, NJ
77. Guay DRP. Pharmacokinetics and pharmacodynamics of ofloxacin in urinary tract infections. In: Penetration: international update on ofloxacin and levofloxacin. Tokyo: Biomedis, 1997: 26-33
78. Vance-Bryan K, Guay DRP, Rotschafer JC. Clinical pharmacokinetics of ciprofloxacin. Clin Pharmacokinet 1990; 19 (6): 434-61
79. Martin SJ, Meyer JM, Chuck SK, et al. Levofloxacin and sparfloxacin: new quinolone antibiotics. Ann Pharmacother 1998 Mar; 32: 320-36
80. Stein GE. Pharmacokinetics and pharmacodynamics of newer fluoroquinolones. Clin Infect Dis 1996; 23 Suppl. 1: S19-24
81. Garcia I, Pascual A, Salvador J, et al. Effect of paclitaxel alone or in combination on the intracellular penetration and activity of quinolones in human neutrophils. J Antimicrob Chemother 1996 Nov; 38: 859-63
82. Labro MT, Vazifeh D, Bryskier A. Levofloxacin uptake by human polymorphonuclear neutrophils in vitro [abstract]. 20th International Congress of Chemotherapy 1997 Jun 29: 97
83. Vazifeh D, Bryskier A, Labro MT. Investigation of the mechanism underlying levofloxacin uptake by human polymorphonuclear neutrophils [abstract no. A74]. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy; Toronto; 1997 Sep 28-Oct 1
84. Honeybourne D, Andrews JM, Jevons G, et al. Penetration of levofloxacin (HR355) into lung tissues after a single 500mg oral dose [abstract no. P377]. 8th European Congress of Clinical Microbiology and Infectious Diseases; Lausanne, Switzerland. 1997 May 25-8
85. Gisclon LG, Curtin CR, Chien SC, et al. The pharmacokinetics (PK) of levofloxacin (LVFX) in subjects with renal impairment, and in subjects receiving hemodialysis or continuous ambulatory peritoneal dialysis [abstract]. 36th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1996 Sep 15; 3
86. Chadwick PR, Marshall B, Keaney MGL, et al. Making real sense of MRSA [letter]. Lancet 1996 Nov 30; 348: 1525
87. Preston SL, Drusano GL, Berman AL, et al. Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. JAMA 1998; 279 (2): 125-9
88. File JTM, Segreti J, Dunbar L, et al. A multicenter, randomized study comparing the efficacy and safety of intravenous and/or oral levofloxacin versus ceftriaxone and/or cefuroxime axetil in treatment of adults with community-acquired pneumonia. Antimicrob Agents Chemother 1997 Sep; 41: 1965-72
89. Carbon C, Members of the International Study Group. Comparative study of levofloxacin and co-amoxiclav in the treatment of community-acquired pneumonia in adults [abstract no. LM70]. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto; 1997 Sep 28-Oct 1
90. Carbon C, Zeimen M, Rangaraj M, et al. Evaluation of the efficacy and safety of oral levofloxacin 500 mg once daily *vs* 500 mg twice daily *vs* amoxicillin/clavulanic acid 500/125 thrice daily for 7 to 10 days in the treatment of community-acquired pneumonia in adults: a double-blind, double-dummy, multinational, multicentre, comparative study. Hoechst Marion Roussel, (data on file)
91. Norrby RS, Petermann W, Willcox PA, et al. Levofloxacin versus ceftriaxone in the treatment of pneumonia in hospitalised patients [abstract no. T108]. Antiinfect Drugs Chemother 1998; 16 Suppl. 1: 62
92. Hoechst Marion Roussel. Open, controlled, randomised, multinational, comparative study of the efficacy, safety and tolerance of levofloxacin (HR355) versus ceftriaxone in the treatment of hospitalised patients with pneumonia. HR335/2/MN/301/LR. Data on file, Hoechst AG, Frankfurt am Main, Germany
93. RW Johnson Pharmaceutical Research Institute. Statistical review of pneumonia study M92-075. Data on file
94. RW Johnson Pharmaceutical Research Institute. Statistical review of pneumonia study K90-071. Data on file
95. DeAbate CA, Russell M, McElvaine P, et al. Safety and efficacy of oral levofloxacin versus cefuroxime axetil in acute bacterial exacerbation of chronic bronchitis. Respir Care 1997; 42 (2): 206-13
96. Habib MP, Gentry LO, Rodriguez-Gomez G, et al. Multicenter, randomized study comparing efficacy and safety of oral levofloxacin and cefaclor in treatment of acute bacterial exacerbations of chronic bronchitis. Infect Dis Clin Pract 1998; 7 (2): 101-9
97. Shah PM, Members of the International Study Group. Levofloxacin versus cefuroxime axetil in the treatment of acute axacerbations of chronic bronchitis [abstract no. LM38]. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto; 1997 Sep 28-Oct 1
98. Adelglass J, DeAbate CA, McElvaine P, et al. A comparison of levofloxacin (LVFX) QD and amoxicillin-clavulanate (Amox/Clav) TID for the treatment of acute bacterial sinusitis [abstract no. 290]. Clin Infect Dis 1996 Oct; 23: 913
99. Kahn JB, Rielly-Gauvin K, Demartin EL, et al. Multicenter, open-label, randomized study to compare the safety and efficacy of oral levofloxacin and BIAXIN (Rm) in the treatment of acute maxillary sinusitis in adults [abstract no. 579]. Clin Infect Dis 1997 Aug; 25: 462
100. Gehanno P, French Sinusitis Study Group. Oral levofloxacin, 500 mg once daily, in the treatment of acute maxillary sinusitis [abstract no. T106]. Antiinfect Drugs Chemother 1998; 16 Suppl. 1: 62
101. Gehanno P, Rangaraj M, Lebrun MJ, et al. Once daily 500 mg oral levofloxacin in the treatment of acute maxillary sinusitis. Study no. F/93/355/01. Hoechst-Roussel, France. Data on file, 1998
102. Sydnor TA, Kopp EJ, Anthony KE, et al. Open-label assessment of levofloxacin for the treatment of acute bacterial sinusitis in adults. Ann Allergy Asthma Immunol 1998; 80: 357-62
103. Nichols RL, Smith JW, Gentry LO, et al. Multicenter, randomized study comparing levofloxacin and ciprofloxacin for uncomplicated skin and skin structure infections. South Med J 1998 Dec; 90 (12): 1193-200
104. Nicodemo AC, Robledo JA, Jasovich A, et al. A multicentre, double-blind, randomised study comparing the efficacy and safety of oral levofloxacin versus ciprofloxacin in the treat-

ment of uncomplicated skin and skin structure infections. Int J Clin Pract 1998; 52 (2): 69-74
105. Klimberg IW, Cox II CE, Fowler CL, et al. A controlled trial of levofloxacin and lomefloxacin in the treatment of complicated urinary tract infection. Urology 1998; 51: 610-5
106. Richard GA, Childs S, Fowler C, et al. A comparison of levofloxacin (LVFX) and ciprofloxacin (cipro) for the treatment of complicated urinary tract infections (cUTI) [abstract]. Clin Infect Dis 1996 Oct; 23: 914
107. Richard GA, Klimberg IN, Fowler C, et al. A combined analysis of two studies comparing levofloxacin (LVFX) with two other fluoroquinolones for the treatment of acute pyelonephritis (pyelo) [abstract]. 36th Interscience Conference on Antimicrobial Agents and Chemotherapy 1996 Sep 15: 281
108. Hoechst Marion Roussel. Summary of product specifications; Tavanic 250 mg tablet, Tavanic 500 mg tablet, Tavanic i.v. 500 mg. Data on file
109. Ball P, Tillotson G. Tolerability of fluoroquinolone antibiotics: past, present and future. Drug Saf 1995; 13 (6): 343-58
110. Takada S, Kato M, Takayama S. Comparison of lesions induced by intra-articular injections of quinolones and compounds damaging cartilage components in rat femoral condyles. J Toxicol Environ Health 1994 May; 42: 73-88
111. Kato M, Takada S, Ogawara S, et al. Effect of levofloxacin on glycosaminoglycan and DNA synthesis of cultured rabbit chondrocytes at concentrations inducing cartilage lesions *in vivo*. Antimicrob Agents Chemother 1995 Sep; 39: 1979-83
112. Boccumini L, Fowler C, Campbell T, et al. Photoreaction potential (PR) of orally administered levofloxacin (LVFX) in healthy subjects [abstract]. Clin Infect Dis 1996 Oct; 23: 913
113. Kohno K, Nozaki M, Takeda N, et al. Neuroexcitable effects of levofloxacin, a novel quinolone antibacterial, in concomitant use of non-steroidal anti-inflammatory drugs: the comparative study with other quinolones [in Japanese]. Yakuri to Chiryo 1994 Apr; 22: 1811-21
114. Shiba K, Sakamoto M, Nakazawa Y, et al. Effects of antacid on absorption and excretion of new quinolones. Drugs 1995; 49 Suppl. 2: 360-1
115. Tanaka M, Kurata T, Fujisawa C, et al. Mechanistic study of inhibition of levofloxacin absorption by aluminum hydroxide. Antimicrob Agents Chemother 1993 Oct; 37: 2173-8
116. Shiba K, Sakai O, Shimada J, et al. Effects of antacids, ferrous sulfate, and ranitidine on absorption of DR-3355 in humans. Antimicrob Agents Chemother 1992 Oct; 36: 2270-4
117. Shiba K, Okazaki O, Aoki H, et al. Influence of antacids and ranitidine on the absorption of levofloxacin in men. Drugs 1993; 45 Suppl. 3: 299-300
118. Okimoto N, Niki Y, Soejima R. Effect of Levofloxacin on serum concentration of theophylline [in Japanese]. Chemotherapy 1992 May; 40 (S-3): 68-74
119. Gisclon LG, Curtin CR, Fowler CL, et al. Absence of a pharmacokinetic interaction between intravenous theophylline and orally administered levofloxacin. J Clin Pharmacol 1997 Aug; 37: 744-50
120. Gaitonde MD, Mendes P, House ESA, et al. The effects of cimetidine and probenecid on the pharmacokinetics of levofloxacin (LVFX) [abstract]. 35th Interscience Conference on Antimicrobial Agents and Chemotherapy 1995 Sep 17: 8
121. Liao S, Palmer M, Fowler C, et al. Absence of an effect of levofloxacin on warfarin pharmacokinetics and anticoagulation in male volunteers. J Clin Pharmacol 1996 Nov; 36: 1072-7
122. Chien SC, Chow AT, Rogge MC. Pharmacokinetics and safety of oral levofloxacin in human immunodeficiency virus-infected individuals receiving concomitant zidovudine. Antimicrob Agents Chemother 1997 Aug; 41: 1765-9
123. Doose DR, Walker SA, Chien SC, et al. Levofloxacin does not alter cyclosporine disposition. J Clin Pharmacol 1998; 38: 90-3
124. Anonymous. The choice of antibacterial drugs. Med Lett Drugs Ther 1998 Mar 27; 40 (1023): 33-42
125. Bartlett JG, Breiman RF, Mandell LA, et al. Guidelines from the Infectious Diseases Society of America. Community-acquired pneumonia in adults: guidelines for management. Clin Infect Dis 1998; 26: 811-38
126. File TM, Tan JS. Treatment of skin and soft-tissue infections. Am J Surg 1995 May; 169 Suppl. 5a: 27S-33S

Correspondence: *Heather D. Langtry*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz