ADIS DRUG EVALUATION

Drugs 2005; 65 (1): 121-136
0012-6667/05/0001-0121/$39.95/0



# Amoxicillin/Clavulanic Acid 2000mg/125mg Extended Release (XR)

## A Review of its Use in the Treatment of Respiratory Tract Infections in Adults

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**Data Selection**

**Sources:** Medical literature published in any language since 1980 on amoxicillin/clavulanic acid, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). 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 Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.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:** Medline search terms were 'amoxicillin clavulanate' or 'amoxicillin clavulanic acid' and ('extended release' or 'slow release' or 'controlled release' or 'XT' or 'XR' or 'pharmacokinetically enhanced'). EMBASE search terms were 'amoxicillin clavulanic acid' or 'amoxicillin clavulanate' and ('extended release' or 'slow release' or 'controlled release' or 'pharmacokinetically enhanced'). AdisBase search terms were 'amoxicillin clavulanic acid' or 'amoxicillin clavulanate' and ('extended release' or 'slow release' or 'controlled release' or 'XT' or 'XR' or 'pharmacokinetically enhanced'). Searches were last updated 29 November 2004.

**Selection:** Studies in adult patients with respiratory tract infections who received extended-release amoxicillin/clavulanic acid 2000mg/125mg. 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:** Amoxicillin/clavulanic acid, community-acquired pneumonia, acute sinusitis, acute exacerbations of chronic bronchitis, antimicrobial activity, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

## Contents

## Summary

**Abstract**

Amoxicillin/clavulanic acid 2000mg/125mg extended release (Augmentin XR™), referred to herein as amoxicillin/clavulanic acid XR, is a pharmacokinetically enhanced formulation designed to provide more effective therapy in adults and adolescents than conventional formulations against community-acquired respiratory tract pathogens, particularly *Streptococcus pneumoniae*, with reduced susceptibility to amoxicillin.

Amoxicillin/clavulanic acid XR maintains plasma amoxicillin concentrations above 4 μg/mL for a mean of 49% of the dosing interval indicating that it would be highly effective against *S. pneumoniae* strains with minimum inhibitory concentrations (MICs) above the National Committee for Clinical Laboratory Standard's amoxicillin ± clavulanic acid susceptibility breakpoint of ≤2 μg/mL. Amoxicillin/clavulanic acid XR is at least as effective as conventional amoxicillin/clavulanic acid formulations, levofloxacin and clarithromycin in treating community-acquired pneumonia, acute bacterial sinusitis or acute exacerbations of chronic bronchitis, and has a tolerability profile comparable to that of conventional amoxicillin/clavulanic acid formulations. While the incidence of amoxicillin- or multidrug-resistant *S. pneumoniae* is not currently sufficient in most regions to warrant the routine empirical use of amoxicillin/clavulanic acid XR, the drug would be extremely useful in those regions with a high incidence of resistant pathogens or in selected patients (i.e. those with *S. pneumoniae* isolates having amoxicillin MICs ≥2 μg/mL but ≤4 μg/mL).

**Pharmacological Properties**

Amoxicillin/clavulanic acid XR consists of a bilayer tablet with one layer containing immediate-release amoxicillin trihydrate plus clavulanic acid, while the other layer contains sustained-release sodium amoxicillin. Each dose (two tablets) contains amoxicillin 2000mg and clavulanic acid 125mg.

In healthy volunteers, single-dose amoxicillin/clavulanic acid XR displayed a delayed absorption phase in addition to the immediate absorption phase and maintained plasma concentrations of amoxicillin ≥4 μg/mL for 49.4% of the 12-hour dosing interval, indicating potential high-level efficacy against pathogens with amoxicillin MICs ≤4 μg/mL. The pharmacokinetic properties of amoxicillin and clavulanic acid were not otherwise different from those of conventional amoxicillin/clavulanic acid formulations.

**Therapeutic Efficacy**

Amoxicillin/clavulanic acid XR administered twice daily for 7–10 days was at least as effective as conventional amoxicillin/clavulanic acid 875mg/125mg two or three times daily or 1000mg/125mg three times daily for 7–10 days in the treatment of community-acquired pneumonia in randomised, double-blind trials. Amoxicillin/clavulanic acid XR provided clinical success rates in the per-protocol populations of 86–95% at the test-of-cure visit compared with 88–93% for the conventional formulations.

In the treatment of patients with acute bacterial sinusitis, amoxicillin/clavulanic acid XR for 10 days was at least as effective as levofloxacin 500mg once daily for 10 days. The combined clinical and radiological success rate in the intent-to-

 

treat population was 84% with either amoxicillin/clavulanic acid XR or levofloxacin.

Amoxicillin/clavulanic acid XR for 5–7 days was at least as effective as levofloxacin 500mg once daily, clarithromycin 500mg twice daily or amoxicillin/clavulanic 875mg/125mg twice daily for 7 days in the treatment of acute exacerbations of chronic bronchitis in adults. Amoxicillin/clavulanic acid XR produced clinical success rates in the per-protocol populations of 83–93% compared with 86–91% for the comparators.

All patients with penicillin- or amoxicillin-resistant *S. pneumoniae* isolates and receiving amoxicillin/clavulanic acid XR were judged to be clinical and/or bacteriological successes at follow-up.

**Tolerability**

The tolerability profile of amoxicillin/clavulanic acid XR did not differ significantly from that of conventional amoxicillin/clavulanic acid. Diarrhoea was the most frequent adverse event, occurring in 11–17% of patients. Most adverse events were of mild-to-moderate severity and resulted in discontinuation of therapy in 2–6% of patients.

## 1. Introduction

The combination of amoxicillin with the β-lactamase inhibitor clavulanic acid (clavulanate potassium) has, for over two decades, effectively extended the spectrum of activity of the semisynthetic oral aminopenicillin to include β-lactamase-producing, penicillin-resistant pathogens, in an era of rapidly developing antimicrobial resistance.[1] Amoxicillin/clavulanic acid is a widely used oral therapy that is effective in the treatment of the most common infections encountered in general practice.[2,3] It is now most commonly used for the empirical treatment of bacterial respiratory tract infections and acute otitis media.[4]

Amoxicillin/clavulanic acid is available in a variety of different oral formulations with the amoxicillin content ranging from 125mg to 1000mg, and with amoxicillin : clavulanic acid ratios ranging from 2 : 1 up to 14 : 1.[3] Most formulations now contain a standard dose of clavulanic acid of 125mg for adults which is considered adequate to fully inhibit the β-lactamase enzymes produced by the common target pathogens.[4]

A new pharmacokinetically enhanced, extended-release formulation of amoxicillin/clavulanic acid (Augmentin XR™)[1], hereafter referred to in this review as amoxicillin/clavulanic acid XR, has been developed to provide more effective therapy against pathogens with reduced susceptibility to amoxicillin.[5,6] Amoxicillin/clavulanic acid XR consists of a bilayer tablet, with one layer containing immediate-release amoxicillin trihydrate (562.5mg) and clavulanic acid (62.5mg), and the other layer containing sustained-release sodium amoxicillin (437.5mg). Each tablet contains 1000mg of amoxicillin and 62.5mg of clavulanic acid (16 : 1 ratio).[5] The recommended dosage is two tablets (amoxicillin/clavulanic acid 2000mg/125mg extended release) twice daily. The formulation is designed to maintain high plasma concentrations of amoxicillin for a greater proportion of the dosing interval than is achievable with conventional formulations of the drug, since the bacteriological efficacy of a β-lactam antibacterial is a direct function of the time that the plasma concentration of free drug remains above the minimum inhibitory concentration (MIC) for the pathogen.[7]

The antibacterial activity, pharmacokinetic properties and therapeutic use of amoxicillin/clavulanic acid in patients with bacterial infections are well established.[2,3] This article reviews data rele-

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

vant to the use of amoxicillin/clavulanic acid XR in patients with respiratory tract infections, with a particular emphasis on patients with community-acquired pneumonia, acute bacterial sinusitis and acute exacerbations of chronic bronchitis.

## 2. Antibacterial Activity

Amoxicillin/clavulanic acid has a broad spectrum of activity against Gram-negative and Gram-positive aerobic and anaerobic bacteria, especially against β-lactamase-producing strains, as reviewed previously in *Drugs*.[2,3] The activity of amoxicillin/clavulanic acid has generally been retained against most of the targeted pathogens throughout the many years of the drug's clinical use since it was first introduced in 1981.[8]

Amoxicillin/clavulanic acid XR is being targeted for the treatment of community-acquired respiratory tract infections in adults, such as community-acquired pneumonia, acute exacerbations of chronic bronchitis and acute bacterial sinusitis (rhinosinusitis) [section 4]. These infections are most commonly caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *H. parainfluenzae*, *Klebsiella pneumoniae* and *Staphylococcus aureus*.[4] Amoxicillin/clavulanic acid XR is specifically aimed at infections caused by *S. pneumoniae* with reduced susceptibility to amoxicillin or β-lactamase-producing strains of the other common pathogens. In the US, infections caused by penicillin-resistant *S. pneumoniae* (i.e. penicillin MICs ≥2 μg/mL, but <4 μg/mL) are identified as being appropriate for treatment with amoxicillin/clavulanic acid XR (see section 6) on the basis of positive correlations between penicillin resistance and reduced amoxicillin susceptibility.[6]

The current National Committee for Clinical Laboratory Standards' (NCCLS) breakpoint MICs of penicillin for susceptible, intermediate and resistant categories of *S. pneumoniae* are ≤0.06, 0.12–1.0 and ≥2 μg/mL, respectively, compared with ≤2, 4 and ≥8 μg/mL for amoxicillin ± clavulanic acid.[9] A susceptible breakpoint MIC of ≤4 μg/mL (relative to the amoxicillin component) against *S. pneumoniae* has been proposed for the new pharmacokinetically enhanced amoxicillin/clavulanic acid XR formulation (compared with ≤2 μg/mL for conventional amoxicillin/clavulanic acid), based on its pharmacokinetic/pharmacodynamic (PK/PD) properties (section 3).[5] The NCCLS breakpoint MICs of conventional amoxicillin ± clavulanic acid for *Haemophilus* spp. are ≤4 μg/mL for susceptible and ≥8 μg/mL for resistant.[9] There are no breakpoint MICs defined by the NCCLS for *M. catarrhalis*.

The *in vitro* antimicrobial activity of amoxicillin/clavulanic acid XR against the most common respiratory pathogens as determined by the worldwide surveillance conducted by the Alexander Project between 1998 and 2000 is shown in table I.[10]

The relationship between penicillin and amoxicillin resistance of *S. pneumoniae* was assessed in 22 penicillin-resistant isolates from patients with community-acquired pneumonia and 26 isolates

**Table I.** *In vitro* antimicrobial activity of amoxicillin/clavulanic acid 2000mg/125mg extended release (AMC XR) against worldwide isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* between 1998 and 2000[10]

| Organism | $MIC_{90}$ value (μg/mL) [% susceptibility[a]] | | | | | | |
|---|---|---|---|---|---|---|---|
| (no. of isolates) | AMC XR | AMC | AMX | CRO | LVX | AZM | SXT |
| *S. pneumoniae* (6512–8882) | 2 [97.9] | 2 [95.5] | 2 [95.1] | 1 [95.1] | 1 [98.9] | >32 [74.3] | 8 [63.3] |
| *H. influenzae* (5651–8523) | 1 [99.6] | 1 [98.1] | >16 [81.6] | 0.008 [100] | 0.015 [99.9] | 2 [<1.2] | >4 [78.3] |
| *M. catarrhalis* (421–874) | 0.25 [100] | 0.25 [100] | 16 [22.7] | 1 [97.4] | 0.06 [>99.5] | 0.12 [99.3] | 1 [72.0] |

a Percentage of isolates considered to be susceptible to the tested antibacterial, using pharmacokinetic/pharmacodynamic susceptibility breakpoint MICs (AMC XR ≤4 μg/mL; AMC, AMX ≤2 μg/mL; CRO ≤1 μg/mL; LVX ≤2 μg/mL; AZM ≤0.12 μg/mL; SXT ≤0.5 μg/mL).

**AMC** = amoxicillin/clavulanic acid; **AMX** = amoxicillin; **AZM** = azithromycin; **CRO** = ceftriaxone; **LVX** = levofloxacin; **SXT** = cotrimoxazole (sulfamethoxazole/trimethoprim).

from patients with acute bacterial sinusitis participating in clinical trials of amoxicillin/clavulanic acid XR.[11] Twenty-one of the 22 isolates from patients with pneumonia had amoxicillin MICs that were within a single dilution step (plus or minus) of the MIC for penicillin. That is, of 16 isolates with a penicillin MIC of 2 μg/mL, ten had an amoxicillin MIC of 2 μg/mL, four had an amoxicillin MIC of 1 μg/mL and one each had amoxicillin MICs of 4 and 8 μg/mL. Of the six isolates with a penicillin MIC of 4 μg/mL, two had an amoxicillin MIC of 2 μg/mL, one had an amoxicillin MIC of 4 μg/mL and three had an amoxicillin MIC of 8 μg/mL. A similar distribution of MICs was observed with isolates from patients with sinusitis.[11] As mentioned, on the basis of these correlations between penicillin and amoxicillin MICs, patients with community-acquired pneumonia and acute bacterial sinusitis considered appropriate for receiving treatment with amoxicillin/clavulanic acid XR are identified in the US as those having infections caused by penicillin-resistant *S. pneumoniae* (penicillin MIC ≥2 μg/mL).[6] For *S. pneumoniae* isolates with a penicillin MIC of 4 μg/mL, there was a higher probability that the amoxicillin MIC might be one dilution step higher (i.e. 8 μg/mL).[11] Therefore, the US FDA does not recommend the use of amoxicillin/clavulanic acid XR for the treatment of infections caused by penicillin-resistant *S. pneumoniae* with penicillin MICs ≥4 μg/mL.[6]

Using susceptibility data for respiratory isolates derived from the Alexander Project surveillance during 2001, it was determined that 88.4% of penicillin-nonsusceptible *S. pneumoniae* isolates (penicillin MIC ≥0.12 μg/mL) collected worldwide (n = 829) were susceptible to amoxicillin/clavulanic acid using the NCCLS MIC breakpoint for amoxicillin ± clavulanic acid of ≤2 μg/mL.[12] However, 94.3% of isolates were susceptible to amoxicillin/clavulanic acid XR at the higher PK/PD-based MIC breakpoint of ≤4 μg/mL proposed for this formulation.

The bactericidal effects of amoxicillin against *S. pneumoniae* strains with different amoxicillin MICs were determined in an *in vitro* kinetic model designed to mimic the amoxicillin exposure associated with pharmacokinetically enhanced amoxicillin/clavulanic acid XR.[13] The time periods that the amoxicillin concentration stayed above the MIC (T > MIC) were 73%, 63%, 53% and 43% of the 24-hour dosing interval for strains with amoxicillin MICs of 1, 2, 4 and 8 μg/mL, respectively (see section 3 for data in healthy volunteers). Two simulated 12-hourly doses resulted in complete killing (at 14–15 hours) of the strains with amoxicillin MICs of 1 and 2 μg/mL. Regrowth after the second dose occurred for the strains with MICs of 4 and 8 μg/mL, although the level of regrowth was lower for the strain with an MIC of 4 μg/mL than for the strain with an MIC of 8 μg/mL (4 vs 6–7 $\log_{10}$ CFU/mL).[13]

A similar *in vitro* kinetic model was used to compare amoxicillin/clavulanic acid XR (2000mg/125mg twice daily) with two conventional amoxicillin/clavulanic acid formulations (875mg/125mg twice daily and 500mg/125mg three times daily) for bactericidal activity against β-lactamase-producing *H. influenzae* strains with amoxicillin ± clavulanic acid MICs of 0.5 or 0.75 μg/mL.[14] Neither conventional formulation, with T > MIC values of 38–50% in the simulation, provided a complete bactericidal effect at 24 hours. In contrast, the model simulating amoxicillin/clavulanic acid XR, with T > MIC values of 73–79%, showed a complete bactericidal effect after the second 12-hourly dose. Clavulanic acid was detectable for only 45% of the 24-hour interval.[14]

Another comparison using an *in vitro* kinetic model showed that amoxicillin/clavulanic acid XR had similar 24-hour bactericidal effects to amoxicillin/clavulanic acid 875mg/125mg against *S. pneumoniae* with amoxicillin ± clavulanic acid MICs <5 μg/mL or *H. influenzae* with MICs of 2 or 5 μg/mL.[15] However, amoxicillin/clavulanic acid XR displayed greater bactericidal effects than the conventional formulation against *S. pneumoniae* with amoxicillin ± clavulanic acid MICs ≥6 μg/mL and against a high inoculum ($10^8$ CFU/mL), but not a low inoculum ($10^6$ CFU/mL), of the *H. influenzae* strain with an amoxicillin ± clavulanic acid MIC of 5 μg/mL.[15] The maximum bactericidal response

occurred at a T > MIC of 50–60% for both bacterial species and both inocula.

In experimental respiratory tract infections caused by *S. pneumoniae* in rats, simulated human administration of amoxicillin/clavulanic acid XR 2000mg/125mg twice daily for 3 days was at least as effective as and often superior to the comparators (simulated human amoxicillin/clavulanic acid 875mg/125mg twice or three times daily, amoxicillin/clavulanic acid 1000mg/125mg three times daily, azithromycin 1000mg on day 1 then 500mg once daily, and levofloxacin 500mg once daily for 3 days).[16] The six *S. pneumoniae* strains tested were penicillin-resistant and had amoxicillin MICs of 4 or 8 μg/mL, and four strains were also resistant to macrolides. Amoxicillin/clavulanic acid XR displayed a significantly ($p < 0.01$) greater bactericidal effect than all comparators except levofloxacin against strains with an amoxicillin MIC of 8 μg/mL. Against strains with an amoxicillin MIC of 4 μg/mL, amoxicillin/clavulanic acid XR was superior ($p < 0.01$) to levofloxacin, azithromycin and amoxicillin/clavulanic acid 875mg/125mg twice daily. These results support a susceptible breakpoint MIC of at least 4 μg/mL for amoxicillin/clavulanic acid XR (see also section 3).[16]

Amoxicillin/clavulanic acid XR also produced a marked bactericidal effect (3-log reduction in bacterial numbers) in experimental respiratory tract infections (rats) caused by β-lactamase-negative, ampicillin-resistant *H. influenzae* with an amoxicillin MIC of 4 μg/mL.[17]

## 3. Pharmacokinetic Properties

The pharmacokinetic properties of single-dose oral amoxicillin/clavulanic acid 2000mg/125mg XR have been assessed in 55 healthy adult volunteers.[5] A mean maximum plasma amoxicillin concentration ($C_{max}$) of 17 μg/mL was attained at a median time ($t_{max}$) of 1.5 hours after oral administration. The mean area under the amoxicillin plasma concentration-time curve extrapolated from time zero to infinity ($AUC_\infty$) was 71.6 μg • h/mL. The amoxicillin plasma concentration-time curve displayed a definite shoulder indicating a secondary absorption phase (related to the sustained-release amoxicillin layer) that occurred after approximately 3–4 hours. The mean time that the plasma amoxicillin concentration remained above 4 μg/mL (T > MIC of 4 μg/mL) was 5.93 hours which was equivalent to 49.4% (standard deviation 10.2%) of the 12-hour dosing interval, suggesting a potential high level of efficacy against pathogens with amoxicillin MICs ≤4 μg/mL. According to the same plasma concentration-time curve, amoxicillin concentrations above 8 μg/mL would appear to be maintained for 4.48 hours or approximately 37% of the dosing interval.[5] Conventional immediate-release amoxicillin/clavulanic acid containing 2000mg of amoxicillin achieved a T > MIC of 4.9 hours compared with 6.3 hours for amoxicillin/clavulanic XR (values estimated from a graph) in seven subjects who received both formulations in a crossover study.[5] The mean terminal elimination half-life of amoxicillin after administration of amoxicillin/clavulanic acid XR was 1.27 hours, similar to that in conventional formulations (1.0–1.3 hours).[2,3] The serum protein binding of amoxicillin/clavulanic acid XR is low (≈18% of amoxicillin bound). Amoxicillin readily diffuses into most tissues and fluids, but does not readily cross the blood-brain barrier.[6,18]

The pharmacokinetic properties of the clavulanic acid component in amoxicillin/clavulanic acid XR were unaltered compared with conventional formulations containing the same dose (125mg) of clavulanic acid. The mean $C_{max}$ was 2.05 μg/mL, the median $t_{max}$ was 1.03 hours, the mean $AUC_\infty$ was 5.29 μg • h/mL and the mean elimination half-life was 1.03 hours with amoxicillin/clavulanic acid XR.[5]

The absorption of amoxicillin is decreased when amoxicillin/clavulanic acid XR is administered in the fasted state, while the absorption of clavulanic acid is decreased when administered with a high-fat meal.[6] The absorption and elimination of amoxicillin/clavulanic acid XR are unaffected by the administration of antacid.[6] As with conventional formulations, the clearance of amoxicillin is predominantly renal, with 60–80% of the dose being excreted unchanged in the urine, while that of clavulanic acid is

only partly renal (30–50%).[6] Concomitant administration of probenecid delays the excretion of amoxicillin, but not clavulanic acid.[6]

## 4. Therapeutic Efficacy

Not all formal clinical trials assessing the efficacy of amoxicillin/clavulanic acid 2000mg/125mg XR have been published. There are seven published studies assessing the therapeutic efficacy of amoxicillin/clavulanic acid XR in adults and adolescents,[19-25] three of which are published in full (studies 556,[19] 557[24] and 600[25]), while data from four additional efficacy trials (studies 546, 547, 548 and 550) are available in the US FDA's medical review of the New Drug Application for amoxicillin/clavulanic acid XR.[11]

The efficacy of amoxicillin/clavulanic acid XR in the treatment of community-acquired pneumonia has been assessed in four randomised, double-blind, multicentre comparisons with conventional formulations of amoxicillin/clavulanic acid[11,19,24,25] and in one noncomparative study[11] (section 4.1). There are three trials in patients with acute bacterial sinusitis, one being a randomised, double-blind, multicentre comparison with levofloxacin,[11] while two are noncomparative studies,[20,23] one of which is an interim analysis[23] (section 4.2). There are three studies in patients with acute exacerbations of chronic bronchitis, all of which are randomised, double-blind, multicentre comparisons with levofloxacin,[21] clarithromycin[11] or conventional amoxicillin/clavulanic acid[22] (section 4.3).

In addition to trial reports, there are several pooled analyses focusing specifically on infections caused by *S. pneumoniae*,[26-29] the largest of which includes combined data from nine clinical trials and is the only one published in full (section 4.4);[26] the analyses that are only available as abstracts are not discussed further in this section.

Where stated, comparative trials were designed as non-inferiority trials. A conclusion of non-inferiority of amoxicillin/clavulanic acid XR relative to the comparator was drawn if the lower limit of the two-sided 95% confidence interval (CI) for the difference between treatments (amoxicillin/clavulanic acid XR response minus the comparator response) was no less than −10%[11,21,25] or −15%.[11,19,24]

### 4.1 Community-Acquired Pneumonia

The primary efficacy endpoint of the four comparative trials in adults and adolescents (aged 16–94 years) with community-acquired pneumonia was the clinical success rate at the test-of-cure visit (day 28–35[19,24] or day 16–37[11,25]), while that for the noncomparative study was the per-patient bacteriological success rate at test-of-cure follow-up (day 16–37).[11] Clinical success was defined as sufficient improvement or resolution of signs and symptoms of pneumonia, such that no additional antibacterial therapy was necessary. Bacteriological success was defined as eradication of pathogens or presumed eradication based on successful clinical outcome in the absence of an evaluable sputum or respiratory sample, with no superinfection or new infection. Both intent-to-treat (ITT) and per-protocol analyses were performed. The primary endpoint was related to the per-protocol population in the comparative trials,[11,19,24] and to the ITT population in the noncomparative trial.[11] Prestudy typical pathogens were isolated from only a small proportion (19–33%) of patients.[11,19,24,25] In all studies, *S. pneumoniae* was the most frequently isolated typical pathogen (36–57% of bacteriologically confirmed patients), followed by *H. influenzae* (21–41%).[11,19,24,25]

Amoxicillin/clavulanic acid XR twice daily for 7–10 days was at least as effective as conventional amoxicillin/clavulanic acid 875mg/125mg twice or three times daily, or 1000mg/125mg three times daily in patients with community-acquired pneumonia (table II); the lower limits of the 95% CI for the treatment differences were consistently greater than the predefined non-inferiority limit of −10% or −15% in all four comparative trials for both the per-protocol and ITT populations.[11,19,24,25] The clinical success rates with amoxicillin/clavulanic acid XR were 78–85% in the ITT populations and 86–95% in the per-protocol populations. These clinical response rates were mirrored by the radiological success rates (table II). The bacteriological success

**Table II.** Efficacy of amoxicillin/clavulanic acid 2000mg/125mg extended release (AMC XR) in the treatment of community-acquired pneumonia in adults and adolescents (aged 16–94 years). Summary of clinical trials, consisting of four randomised, double-blind, multicentre comparisons with conventional amoxicillin/clavulanic acid (AMC)[11,19,24,25] and one noncomparative study[11]

| Study | Dosage (mg) [duration (d)] | No. of pts (ITT/PP)[a] | Clinical success rate (% of pts)[b] | | Radiological success rate (% of pts)[b,c] | | Per-pt bacteriological success rate (no. of pts) [%][b] | |
|---|---|---|---|---|---|---|---|---|
| | | | ITT | PP | ITT | PP | ITT | PP |
| **Comparisons with conventional AMC** | | | | | | | | |
| File et al.[25] | AMC XR 2000/125 bid [7] | 322/247 | 85.1 | 90.3[d] | 87.3 | 93.1 | 73/87 [83.9] | 58/67 [86.6] |
| (600 Study) | AMC 875/125 bid [7] | 311/226 | 78.1 | 87.6[d] | 81.7 | 90.3 | 49/73 [67.1] | 40/51 [78.4] |
| Garau et al.[24] | AMC XR 2000/125 bid [7–10] | 158/114 | 84.8 | 94.7[d] | 82.3 | 94.7 | 21/30 [70.0] | 17/20 [85.0] |
| (Study 557) | AMC 875/125 tid [7–10] | 161/116 | 77.0 | 88.8[d] | 77.6 | 87.9 | 20/30 [66.7] | 17/22 [77.3] |
| Petitpretz et | AMC XR 2000/125 bid [10] | 169/118 | 81.1 | 91.5[d] | NR | 92.4 | 37/44 [84.1] | 29/32 [90.6] |
| al.[19] (Study 556) | AMC 1000/125 tid [10] | 175/114 | 85.7 | 93.0[d] | NR | 93.9 | 36/47 [76.6] | 27/32 [84.4] |
| Study 546[11][e] | AMC XR 2000/125 bid [7] | 255/204 | 78.0 | 86.3[d] | NA | NA | 27/39 [69.2] | 25/32 [78.1] |
| | AMC 875/125 bid [7] | 259/204 | 82.6 | 91.2[d] | NA | NA | 25/30 [83.3] | 22/26 [84.6] |
| **Noncomparative study** | | | | | | | | |
| Study 547[11][e,f] | AMC XR 2000/125 bid [7] | 420/333 | 82.6 | 89.2 | NA | NA | 119/142 [83.8][d] | 105/119 [88.2] |

a Pt numbers apply only to the clinical and radiological response assessment groups, not to the bacteriological assessment groups.

b Determined at the test-of-cure visit on day 28–35.

c Radiological success was defined as improvement or resolution of radiological signs of pneumonia.

d Primary efficacy endpoint.

e Data from studies 546 and 547 were presented in the US FDA's medical review of the New Drug Application for amoxicillin/clavulanic acid XR.

f Interim analysis of an ongoing study.

**bid** = twice daily; **ITT** = intent-to-treat population; **NA** = not assessed; **NR** = not reported; **PP** = per-protocol (completers) population; **pts** = patients; **tid** = three times daily.

rates were slightly lower at 69–84% for the ITT populations and 78–91% for the per protocol populations. In the three published studies, penicillin-resistant *S. pneumoniae* strains with amoxicillin ± clavulanic acid MICs of 2–8 μg/mL were isolated from only eight evaluable patients: three with amoxicillin MICs of 2 μg/mL, one with an MIC of 4 μg/mL and two with MICs of 8 μg/mL treated with amoxicillin/clavulanic acid XR; and one with an MIC of 4 μg/mL and one with an MIC of 8 μg/mL treated with conventional formulations of amoxicillin/clavulanic acid.[19,24,25] All eight of these patients were bacteriological successes at follow-up.

### 4.2 Acute Bacterial Sinusitis

The primary efficacy variable of the comparative trial in patients with acute bacterial sinusitis was the combined clinical and radiological response at the test-of-cure visit on day 17–28 in the per-protocol population,[11] while the primary endpoint of the noncomparative studies was the per-patient bacteriological success rate (pathogen eradication or presumed eradication based on clinical response, without new infection) at the test-of-cure visit (day 17–28) in the bacteriology ITT population.[20,23] Patients were adults and adolescents (aged ≥16[20,23] or ≥18[11] years) with a mean age, where stated, of approximately 40 years.[11,20] Pre-study pathogens, predominantly *S. pneumoniae* and *H. influenzae*, were isolated in 45–52% of patients across the three studies.[11,20,23]

Amoxicillin/clavulanic acid XR twice daily for 10 days was at least as effective as levofloxacin 500mg once daily for 10 days in the treatment of acute bacterial sinusitis (table III); the lower 95% CI (−9.4) for the treatment difference was greater than the predefined non-inferiority limit of −15%.[11] The bacteriological and clinical success rates were consistent in the noncomparative studies at 87–88% (table III). In the published studies, all penicillin-

resistant (penicillin MIC ≥2 μg/mL) *S. pneumoniae* isolates (n = 31), including those with amoxicillin ± clavulanic acid MICs of 4 or 8 μg/mL (n = 6), were bacteriological successes at follow-up.[20,23]

### 4.3 Acute Exacerbations of Chronic Bronchitis

The primary endpoint in the three studies examining the efficacy of amoxicillin/clavulanic acid XR in adult patients with acute exacerbations of chronic bronchitis was the clinical success rate at the test-of-cure visit (day 14–23) [in addition to clinical success at the end of therapy] in the per-protocol population.[11,21,22] A non-inferiority criterion was not specified in one abstract,[22] but for the other two studies was defined as a lower 95% CI for the difference in treatment response rates of not less than −10%.[11,21]

Amoxicillin/clavulanic acid XR twice daily for 5 or 7 days was at least as effective as levofloxacin 500mg once daily, amoxicillin/clavulanic acid 875mg/125mg twice daily or clarithromycin 500mg twice daily for 7 days with respect to clinical response in patients with acute exacerbations of chronic bronchitis (lower 95% CIs of −7.1, −2.2 and −9.1, respectively) [table IV].[11,21,22] The bacteriological success rates in the per-protocol populations at the test-of-cure visit on day 14–23 for amoxicillin/clavulanic acid XR (73-80%) were similar to those of levofloxacin (83%), conventional amoxicillin/clavulanic acid (73%) or clarithromycin (84%) [table IV]. In the studies comparing amoxicillin/clavulanic acid XR with levofloxacin or clarithromycin, *H. influenzae* was the most frequently isolated pathogen.[11] The three patients with penicillin-resistant *S. pneumoniae* and who received treatment with amoxicillin/clavulanic acid XR were clinical and bacteriological successes at the test-of-cure visit.[11,21]

### 4.4 Pooled Analysis

Amoxicillin/clavulanic acid XR was both clinically and bacteriologically (eradication or presumed eradication) successful at follow-up in 60 of 64 (93.7%) and 348 of 363 (95.9%) patients with respiratory tract infections caused by *S. pneumoniae* in comparative (n = 6) and noncomparative studies (n = 3), respectively, from a pooled analysis of nine clinical trials (four in community-acquired pneumonia, three in acute bacterial sinusitis and two in acute exacerbations of chronic bronchitis).[26]

At study entry, 56 *S. pneumoniae* isolates were resistant to penicillin (penicillin MIC ≥2 μg/mL) and nine were also resistant to amoxicillin/clavulanic acid (amoxicillin ± clavulanic acid MICs of 8 μg/

**Table III.** Efficacy of amoxicillin/clavulanic acid 2000mg/125mg extended release (AMC XR) in the treatment of acute bacterial sinusitis in adult and adolescent patients (pts) aged ≥16 or ≥18 years. Summary of clinical efficacy trials (one randomised, double-blind, comparative trial[11] and two noncomparative, multicentre trials[20,23])

| Study | Dosage (mg) [duration (d)] | Combined clinical and radiological success rate (no. of pts) [%][a] | Per-patient bacteriological success rate (no. of pts) [%][b] | Clinical success rate (no. of pts) [%][b] |
|---|---|---|---|---|
| **Comparison with LVX** | | | | |
| Study 550[11][c] | AMC XR 2000/125 bid [10] | 103/123 [83.7][f] | NR | 146/178 [82.0] |
| | LVX 500 od [10] | 118/140 [84.3][f] | NR | 161/182 [88.5] |
| **Noncomparative studies** | | | | |
| Anon et al.[23][d,e] | AMC XR 2000/125 bid [10] | NA | 348/399 [87.2][f] | 676/775 [87.2] |
| Poole et al.[20] (Study 551)[e] | AMC XR 2000/125 bid [10] | NA | 365/415 [88.0][f] | 756/859 [88.0] |

a Determined in the per-protocol population at the test-of-cure visit on day 17–28.

b Determined in the intent-to-treat population at the test-of-cure visit on day 17–28.

c Data from study 550 were presented in the US FDA's medical review of the New Drug Application for amoxicillin/clavulanic acid XR.

d Interim analysis.

e Published as an abstract.

f Primary efficacy endpoint.

**bid** = twice daily; **LVX** = levofloxacin; **NA** = not assessed; **NR** = not reported: **od** = once daily.

**Table IV.** Efficacy of amoxicillin/clavulanic acid 2000mg/125mg extended release (AMC XR) in the treatment of acute exacerbations of chronic bronchitis in adult patients (pts) aged ≥40 years. Summary of randomised, double-blind, multicentre comparisons with levofloxacin (LVX),[21] conventional amoxicillin/clavulanic acid (AMC)[22] or clarithromycin (CLR)[11]

| Study | Dosage (mg) [duration (d)] | Clinical success rate (no. of pts) [%][a,b] | Per-patient bacteriological success rate (no. of pts) [%][a] |
|---|---|---|---|
| Anzueto et al.[21]c (Study 549) | AMC XR 2000/125 bid [7] | 219/255 [85.9] | 52/65 [80.0] |
| | LVX 500 od [7] | 230/264 [87.1] | 49/59 [83.1] |
| Sethi et al.[22]c | AMC XR 2000/125 bid [5] | 332/357 [93.0] | 89/116 [76.7] |
| | AMC 875/125 bid [7] | 322/353 [91.2] | 81/111 [73.0] |
| Study 548[11]d | AMC XR 2000/125 bid [7] | 201/241 [83.4] | 38/52 [73.1] |
| | CLR 500 bid [7] | 224/260 [86.2] | 47/56 [83.9] |

a Determined in the per-protocol population at the test-of-cure visit on day 14–23.

b Primary efficacy endpoint.

c Published as an abstract.

d Data from study 548 were presented in the US FDA's medical review of the New Drug Application for amoxicillin/clavulanic acid XR.

**bid** = twice daily; **od** = once daily.

mL).[26] Twelve penicillin-resistant isolates were of intermediate amoxicillin/clavulanic acid susceptibility (amoxicillin ± clavulanic acid MICs of 4 μg/mL). Clinical and bacteriological success was achieved for 55 (98.2%) of these penicillin-resistant isolates; the one failure being an isolate with an amoxicillin ± clavulanic acid MIC of 8 μg/mL.[26]

The combined clinical and bacteriological success rate at follow-up for the comparators (levofloxacin, clarithromycin, amoxicillin/clavulanic acid 1000mg/125mg or 875mg/125mg) in these trials was 86.5% (45 of 52 patients).[26] Treatment failed in two of four patients with penicillin-resistant isolates. Isolates from both treatment failures were also resistant to erythromycin (erythromycin MIC ≥1 μg/mL).

## 5. Tolerability

The tolerability of amoxicillin/clavulanic acid XR twice daily did not differ significantly from that of conventional amoxicillin/clavulanic acid 875mg/125mg twice or three times daily (figure 1)[24,25] or 1000mg/125mg three times daily (figure 2)[19] in the three fully published clinical trials providing complete tolerability data (see section 4.1 for study details).[19,24,25] Diarrhoea was the most common adverse event, occurring in 11–17% of patients.[19,24,25] Most adverse events in clinical trials were of mild-to-moderate severity.[20,22,24,25] In one study, 7% of amoxicillin/clavulanic acid XR recipients and 6% of amoxicillin/clavulanic acid 1000mg/125mg recipients experienced serious adverse events, although all but two instances (overdose in one patient and persistence of pneumonia in one patient) were considered unrelated to study medication.[19] The proportion of patients withdrawing from therapy as a result of adverse events ranged from 2–6% across the clinical trials.[19-21,23-25,30] In the three studies reporting details, the particular events leading to treatment discontinuation were generally infrequent events, with pneumonia and respiratory disorder being the most common.[19,24,25]

Pooled data from 4144 patients treated with amoxicillin/clavulanic acid XR indicate that the most common adverse events with a possible/probable relationship to drug therapy were diarrhoea (16% of patients), nausea (2%), genital moniliasis (2%) and abdominal pain (2%). Overall, 2% of patients discontinued therapy as a result of drug-related adverse events.[6]

The adverse event profile of amoxicillin/clavulanic acid XR was similar to that of levofloxacin and clarithromycin, although amoxicillin/clavulanic acid XR tended to have a higher incidence of diarrhoea and genital moniliasis than each of the comparators.[11] In one trial, the frequency of adverse events with amoxicillin/clavulanic acid XR was similar to that with levofloxacin during treatment for 7 days (36.2% vs 36.8%), and withdrawal rates as a

result of adverse events were likewise comparable (3.3% vs 3.5%).[21]

## 6. Dosage and Administration

Amoxicillin/clavulanic acid XR is registered in the EU for the treatment of respiratory tract infections (including those caused by penicillin-resistant *S. pneumoniae*) in adults or adolescents aged ≥16 years. It is registered in Belgium (and other European countries) for the treatment of community-acquired pneumonia, acute bacterial sinusitis and acute exacerbations of chronic bronchitis. It has been approved in Spain for the treatment of community-acquired pneumonia caused by susceptible organisms (i.e. amoxicillin MIC ≤4 μg/mL for *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and *S. aureus* [methicillin-susceptible]).[18]

The US FDA has approved amoxicillin/clavulanic acid XR in adults and adolescents for the treatment of acute bacterial sinusitis and community-acquired pneumonia caused by β-lactamase-producing pathogens and *S. pneumoniae* with penicillin MICs ≥2 μg/mL but <4 μg/mL [see section 2].[6]

The recommended dosage is two tablets (2000mg/125mg) administered orally twice daily and preferably taken at the start of a standardised meal (not high-fat).[6,18] The recommended duration of treatment is 7–10 days for community-acquired pneumonia[6,18] and 10 days for acute bacterial sinu-

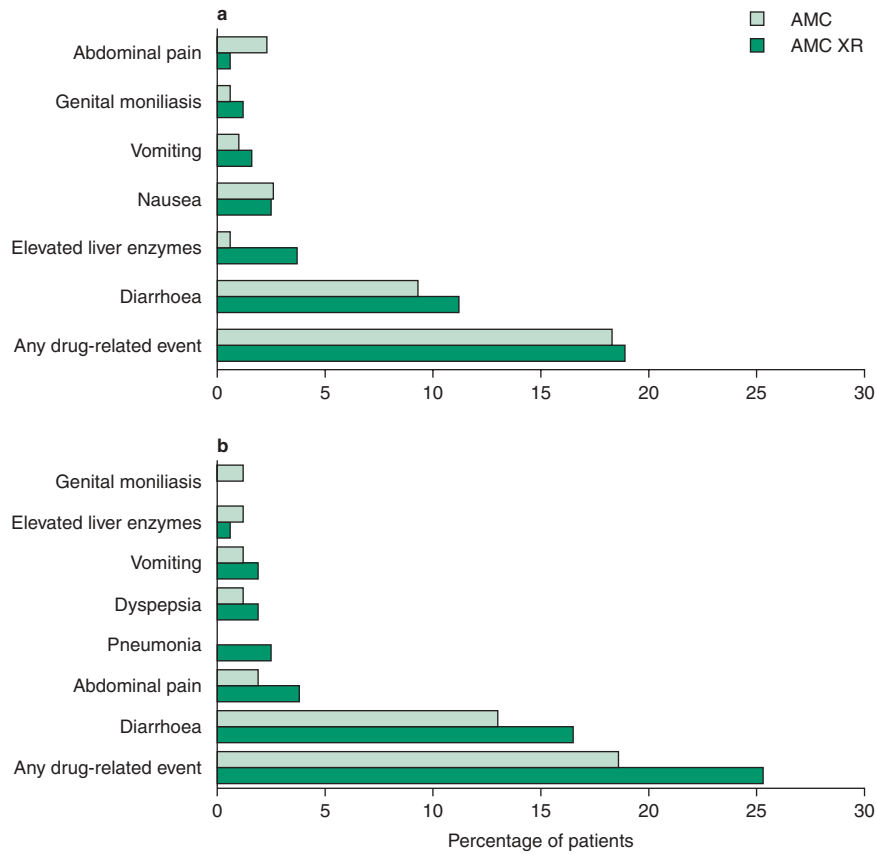


**Fig. 1.** Comparative tolerability of amoxicillin/clavulanic acid 2000mg/125mg extended release (AMC XR) and amoxicillin/clavulanic acid 875mg/125mg (AMC). Adverse events (with a suspected or probable relationship to the study medication) experienced by patients with community-acquired pneumonia in two randomised, double-blind, multicentre trials comparing treatment with AMC XR twice daily with that of conventional AMC twice daily (**a**) [n = 633][25] or three times daily (**b**) [n = 319][24] for 7–10 days.

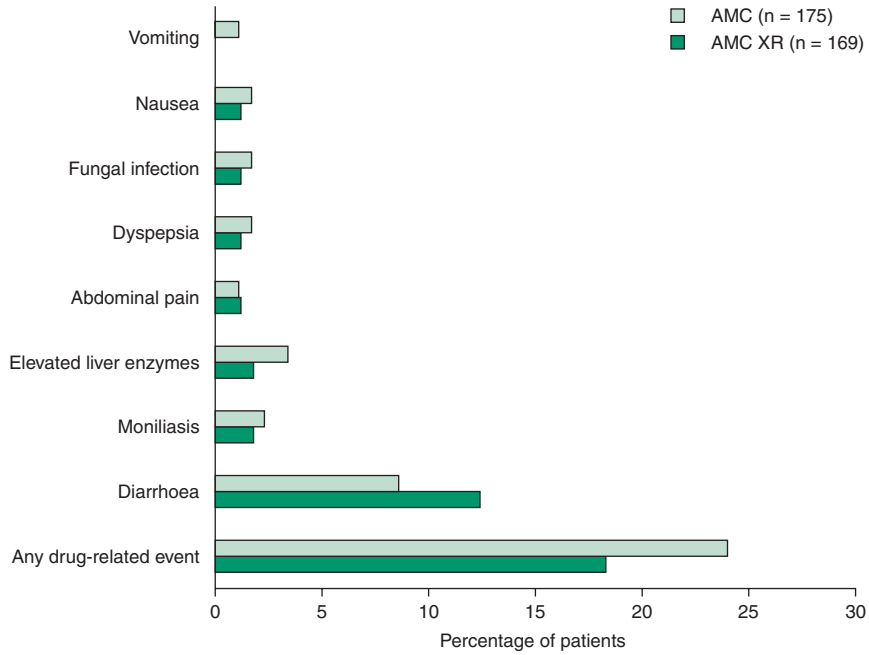


**Fig. 2.** Comparative tolerability of amoxicillin/clavulanic acid 2000mg/125mg extended release (AMC XR) and amoxicillin/clavulanic acid 1000mg/125mg (AMC). Adverse events (with a suspected or probable relationship to the study medication) experienced by patients with community-acquired pneumonia in a randomised, double-blind, multicentre trial comparing treatment with AMC XR twice daily with that of conventional AMC three times daily for 10 days.[19]

sitis.[6] Local prescribing information should be consulted for any contraindications, warnings or recommended dosage adjustments in special patient groups.

## 7. Place of Amoxicillin/Clavulanic Acid XR in the Treatment of Respiratory Tract Infections in Adults

Respiratory tract infections, along with otitis media, account for a high proportion of all antibacterial consumption in the community.[31] The most common bacterial pathogens causing community-acquired respiratory tract infections in adults are *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*.[10] However, it is often difficult to isolate pathogens in these infections and therefore treatment is often empirical.[32] As a result, it is important for prescribing physicians to be aware of local antibacterial resistance patterns of common pathogens in order to ensure appropriate choices of antibacterial agents. Resistance occurs by a variety of adaptive mechanisms. For example, the ability to produce β-lactamase renders most strains of *M. catarrhalis* and certain strains of *H. influenzae* resistant to β-lactam antibacterials such as amoxicillin.

The antimicrobial susceptibility of common respiratory pathogens in adults worldwide has been monitored by the Alexander Project since 1992 and these data have demonstrated increasing resistance to various antibacterials in many countries, although there is much geographical and temporal variation in susceptibility patterns.[10] During the period 1998–2000, *M. catarrhalis* had the least geographical variation in antimicrobial susceptibility and 92.1% of isolates were β-lactamase positive. In contrast, 16.9% of *H. influenzae* isolates were β-lactamase positive overall, but this varied in individual centres from 4.2% (Russia) to 29.6% (USA). The prevalence of penicillin resistance amongst *S. pneumoniae* isolates was 18.2% overall, but varied from 1.1% in Brazil to 69.9% in Hong Kong.[10] Similarly, the overall prevalence of penicillin-resis-

tant *S. pneumoniae* in Western Europe was 13.4%, but was considerably higher in France (40.5%), Spain (26.4%) and Ireland (24.1%), and was notably lower in the Netherlands (1.1%) and Germany (1.9%).[10]

Between 1998 and 2000, *S. pneumoniae* was most susceptible to fluoroquinolones, amoxicillin/clavulanic acid, amoxicillin and ceftriaxone; *H. influenzae* was most susceptible to fluoroquinolones, ceftriaxone, cefixime, amoxicillin/clavulanic acid and chloramphenicol; while *M. catarrhalis* was most susceptible to amoxicillin/clavulanic acid, cefixime, cefdinir, chloramphenicol and fluoroquinolones.[10] Overall, the proportion of worldwide respiratory isolates susceptible to amoxicillin/clavulanic acid was relatively high at 95.5% for *S. pneumoniae*, 98.1–99.6% for *H. influenzae* and 100% for *M. catarrhalis*.[10]

A particular concern has been the rate of development of penicillin-nonsusceptible *S. pneumoniae* in community-acquired respiratory tract infections, along with an increase in the proportion of isolates with decreased susceptibility to amoxicillin.[10,33] Resistance to macrolides (e.g. erythromycin, clarithromycin and azithromycin) parallels that of penicillin, and there is an increasing incidence of *S. pneumoniae* strains resistant to both penicillin and macrolides.[31,34] However, penicillin resistance can usually be overcome by increasing the dosage of penicillin.[33,35] To date, the existence of penicillin-resistant *S. pneumoniae* in respiratory tract infections does not appear to have translated into documented clinical failure when adequate dosages of aminopenicillins have been used.[4,34,35]

Penicillin resistance of *S. pneumoniae* is related to alterations in penicillin-binding proteins and bacterial cell wall structure, not to β-lactamase production.[36] Therefore, there is no theoretical advantage in using amoxicillin/clavulanic acid rather than just amoxicillin against this pathogen. However, since treatment is often empirical, amoxicillin/clavulanic acid provides coverage for β-lactamase-producing strains of the other common respiratory pathogens. Also, clavulanic acid has been shown to enhance the activity of amoxicillin against both penicillin-resistant and penicillin-susceptible *S. pneumoniae* in experimental respiratory infections in the rat,[37] suggesting that clavulanic acid has antibacterial activity independent of β-lactamase inhibition.[1,37]

Amoxicillin/clavulanic acid XR was designed to maintain high plasma concentrations of amoxicillin for a higher than usual proportion of the 12-hour dosing interval in order to more effectively treat infections caused by penicillin-resistant pathogens with reduced susceptibility to amoxicillin. The primary target pathogen appears to be *S. pneumoniae*, for which the current NCCLS amoxicillin ± clavulanic acid susceptibility breakpoint MIC is ≤2 μg/mL. Amoxicillin/clavulanic acid XR achieves amoxicillin concentrations greater than 4 μg/mL for approximately 49% of the dosing interval (section 3) indicating that the drug is likely to be highly effective against strains with an amoxicillin MIC of 4 μg/mL. A T > MIC of ≥40% of the dosing interval for amoxicillin is generally considered necessary to maximise its antibacterial effect against *S. pneumoniae*.[7] Thus, a new susceptibility breakpoint MIC for amoxicillin/clavulanic acid XR of ≤4 μg/mL against *S. pneumoniae* has been proposed (section 2).[5] However, pharmacokinetic studies have not been performed in patient groups (only in volunteers), nor has any Monte Carlo analysis been performed to confirm that most patients would achieve a T > MIC of ≥40% for an MIC of 4 μg/mL.

It is worth noting the results from the Alexander Project surveillance in 1998–2000 for Hong Kong, the centre with the highest prevalence of penicillin-resistant *S. pneumoniae*.[10] Of 193 isolates, 26.4% were susceptible to penicillin, 80.3% were susceptible to amoxicillin, 81.9% were susceptible to conventional amoxicillin/clavulanic acid formulations (NCCLS breakpoint MIC ≤2 μg/mL), while 100% were susceptible to amoxicillin/clavulanic acid XR (PK/PD-based breakpoint MIC ≤4 μg/mL).[10]

Patients infected with penicillin-resistant, amoxicillin-nonsusceptible *S. pneumoniae* are the appropriate target population for treatment with amoxicillin/clavulanic acid XR. The incidence of amoxicillin-nonsusceptible *S. pneumoniae* was <5% globally in 1998–2000[10] and <7% in North America be-

tween 1997 and 2001.[38] While most geographical regions do not yet have incidences of amoxicillin-nonsusceptible *S. pneumoniae* that would appear sufficient to justify the routine empirical use of amoxicillin/clavulanic acid XR, resistance patterns in certain countries, such as Hong Kong, France and Spain, would justify the routine use of high-dose amoxicillin.

Amoxicillin/clavulanic acid XR was at least as effective as levofloxacin, clarithromycin or conventional formulations of amoxicillin/clavulanic acid in the treatment of community-acquired respiratory tract infections (section 4), although no pharmacoeconomic studies have been performed to compare their cost effectiveness. Owing to the extremely low number of *S. pneumoniae* isolates with elevated amoxicillin MICs involved in these therapeutic trials (one to three isolates per study), it was not practical to attempt to demonstrate an enhanced activity of amoxicillin/clavulanic acid XR relative to conventional amoxicillin/clavulanic acid against these pathogens. All patients in whom penicillin-resistant and/or amoxicillin-nonsusceptible *S. pneumoniae* were isolated were consistently classified as clinical and/or bacteriological successes after treatment with amoxicillin/clavulanic acid XR (section 4). The tolerability profile of amoxicillin/clavulanic acid XR was not significantly different from that of conventional amoxicillin/clavulanic acid formulations, levofloxacin or clarithromycin (section 5).

Treatment guidelines vary geographically, but most recommendations include amoxicillin, macrolides, fluoroquinolones, amoxicillin/clavulanic acid, selected cephalosporins, doxycycline and cotrimoxazole (trimethoprim/sulfamethoxazole) as first or second choice antibacterials for treating community-acquired respiratory tract infections such as community-acquired pneumonia,[39-42] acute exacerbations of chronic bronchitis[43] and acute bacterial sinusitis in adults.[44] Resistance of *S. pneumoniae* to doxycycline and cotrimoxazole is becoming widespread.[10] An increasing incidence of *S. pneumoniae* resistant to macrolides is beginning to make these drugs less suitable for empirical therapy in some regions (e.g. Hong Kong, Japan and France).[10] The incidence of resistance to the newer fluoroquinolones is currently low, but is increasing in invasive pneumococci.[45,46] There are fears that widespread use of these drugs, especially if they were to be approved for use in children, could result in the rapid development of resistant *S. pneumoniae*.[32,47] Resistance to amoxicillin amongst *S. pneumoniae* is also low in most regions and high-dose amoxicillin is still often recommended for the empirical treatment of community-acquired pneumonia.[39,41]

Amoxicillin/clavulanic acid XR is registered in different European nations for use in various respiratory tract infections. For instance, in Belgium it is registered for use in community-acquired pneumonia, acute bacterial sinusitis and acute exacerbations of chronic bronchitis, while in Spain it is only registered for use in community-acquired pneumonia. It is approved in the US for the treatment of community-acquired pneumonia and acute bacterial sinusitis. Appropriate patients are identified as those having pathogens resistant to penicillin, on the basis that penicillin-resistance correlates with a high probability of amoxicillin-nonsusceptibility (see section 2).

In conclusion, amoxicillin/clavulanic acid XR maintains plasma amoxicillin concentrations above 4 μg/mL for a mean of 49% of the dosing interval indicating that it would be highly effective against *S. pneumoniae* strains with MICs above the NCCLS amoxicillin ± clavulanic acid susceptibility breakpoint of 2 μg/mL. Amoxicillin/clavulanic acid XR is at least as effective as conventional amoxicillin/clavulanic acid formulations, levofloxacin and clarithromycin in treating community-acquired pneumonia, acute bacterial sinusitis or acute exacerbations of chronic bronchitis, and has a tolerability profile comparable to that of conventional amoxicillin/clavulanic acid formulations. While the incidence of amoxicillin- or multidrug-resistant *S. pneumoniae* is not currently sufficient in most regions to warrant the routine empirical use of amoxicillin/clavulanic acid XR, the drug would be extremely useful in those regions with a high incidence of resistant pathogens or in selected patients (i.e. those with *S.*

*pneumoniae* isolates having amoxicillin MICs ≥2 μg/mL but ≤4 μg/mL).

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