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Cefdinir

A Review of its Use in the Management of Mild-to-Moderate Bacterial Infections

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Data Selection

Sources: Medical literature published in any language since 1980 on cefdinir, 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 Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.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 'cefdinir' or 'BMY-28488' or 'CI-983' or 'FK-482' or 'PD-134393'. EMBASE search terms were 'cefdinir'. AdisBase search terms were 'cefdinir' or 'CI-983' or 'FK-482' or 'PD-134393'. Searches were last updated 8 June 2004.

Selection: Studies in patients with bacterial infections who received cefdinir. 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: Cefdinir, pharmacodynamics, pharmacokinetics, therapeutic use.

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Summary

Abstract

Cefdinir (Omnicef®) is an oral third-generation cephalosporin with good *in vitro* activity against many pathogens commonly causative in community-acquired infections. The drug provides good coverage against *Haemophilus influenzae*, *Moraxella catarrhalis* and penicillin-susceptible *Streptococcus pneumoniae*, the most common respiratory tract pathogens. Cefdinir is stable to hydrolysis by commonly occurring plasmid-mediated β-lactamases and retains good activity against β-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*. The drug distributes into various tissues (e.g. sinus and tonsil) and fluids (e.g. middle ear), and has a pharmacokinetic profile that allows for once- or twice-daily administration.

Cefdinir, administered for 5 or 10 days, has shown good clinical and bacteriological efficacy in the treatment of a wide range of mild-to-moderate infections of the respiratory tract and skin in adults, adolescents and paediatric patients in randomised, controlled trials.

In adults and adolescents, cefdinir is an effective treatment for both lower (acute bacterial exacerbations of chronic bronchitis [ABECB], community-acquired pneumonia) and upper (acute bacterial rhinosinusitis, streptococcal pharyngitis) respiratory tract infections, and uncomplicated skin infections. Its bacteriological and clinical efficacy in patients with lower respiratory tract infections was equivalent to that of comparator agents (cefprozil [bacteriological only], loracarbef, cefuroxime axetil and cefaclor). In one trial in patients with ABECB, cefdinir produced a higher rate of clinical cure than cefprozil (95% CIs indicated nonequivalence). Cefdinir also produced good clinical and bacteriological responses equivalent to responses with amoxicillin/clavulanic acid in patients with acute bacterial rhinosinusitis. In addition, it was at least as effective as penicillin V (phenoxymethylpenicillin) in streptococcal pharyngitis/tonsillitis and as effective as cefalexin in uncomplicated skin infections.

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In paediatric patients aged ≥6 months, cefdinir showed similar efficacy to that of amoxicillin/clavulanic acid or cefprozil in acute otitis media, and cefalexin in uncomplicated skin infections. Cefdinir given for 5 or 10 days was at least as effective as penicillin V for 10 days in patients with streptococcal pharyngitis/tonsillitis.

Cefdinir is usually well tolerated. Diarrhoea was the most common adverse event in trials in all age groups. Although the incidence of diarrhoea in cefdinir recipients was generally higher than in adults and adolescents treated with comparators, discontinuation rates due to adverse events were generally similar for cefdinir and comparator groups.

In conclusion, cefdinir is a third-generation cephalosporin with a broad spectrum of antibacterial activity encompassing pathogens that are commonly causative in infections of the respiratory tract or skin and skin structure. Depending on the infection being treated, cefdinir can be administered as a convenient once- or twice-daily 5- or 10-day regimen. Clinical evidence indicates that cefdinir is an effective and generally well tolerated drug with superior taste over comparator antibacterial agents and is therefore a good option for the treatment of adults, adolescents and paediatric patients with specific mild-to-moderate respiratory tract or skin infections, particularly in areas where β-lactamase-mediated resistance among common community-acquired pathogens is a concern.

Antibacterial Activity

Cefdinir has a broad spectrum of antibacterial activity encompassing a number of Gram-positive and -negative pathogens that are commonly causative in community-acquired respiratory and skin infections. Results of many studies published since 1995 show that cefdinir has good activity against penicillin-susceptible strains of *Streptococcus pneumoniae*, *S. pyogenes* and methicillin-susceptible *Staphylococcus aureus*, including β-lactamase-producers. However, in common with many other β-lactam antibacterials, cefdinir shows less activity against penicillin-intermediate and -resistant pneumococci and is inactive against methicillin-resistant *S. aureus*.

Cefdinir is also active against the important respiratory tract Gram-negative pathogens *Haemophilus influenzae* and *Moraxella catarrhalis*, including β-lactamase-producing strains of both micro-organisms. In addition, the drug shows good *in vitro* activity against *H. parainfluenzae*. Cefdinir is stable to hydrolysis by many plasmid-encoded β-lactamases, including TEM-1, TEM-2, TEM-6, TEM-7, TEM-9, TEM-10, HMS-1, CAZ-2, SHV-1, OXA-1, OXA-2, OXA-3 and P99 type 1a. However, it is susceptible to hydrolysis by TEM-3, TEM-4, TEM-5, PSE-2, P99 type 1c, SHV2, SHV-3, SHV-4, SHV-5, MEN-1, K-1, CARB-1, CARB-2, CARB-3 and OXA-4 β-lactamases.

The bactericidal effect of cefdinir is achieved by its binding to penicillin-binding proteins. This leads to damage of the cell wall, cell lysis and death of susceptible bacteria. Cefdinir is rapidly bactericidal against a number of pathogens at minimum bactericidal concentrations of two to four times the minimum inhibitory concentration. Cefdinir has also shown efficacy in several animal models of infection, including pneumonia caused by *H. influenzae* or penicillin-susceptible strains of *S. pneumoniae* and subcutaneous abscesses induced by *S. aureus*.

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Pharmacokinetic Properties

In adults, mean maximum plasma cefdinir concentrations (C_{max}) were 1.6 and 2.87 mg/L after single doses of 300mg and 600mg at a mean time of ≈3 hours. In paediatric patients, mean cefdinir C_{max} values were 2.3 and 3.86 mg/L approximately 2 hours after administration of 7 and 14 mg/kg doses of the suspension. Cefdinir has a linear pharmacokinetic profile over the 200–400mg dose range, but displays nonlinear pharmacokinetics at a higher dose (600mg). At therapeutic dosages, cefdinir does not accumulate in the plasma of individuals with normal renal function.

Cefdinir has an estimated bioavailability of 21% and 16% after administration of single 300 and 600mg capsules, and an estimated absolute bioavailability of 25% after administration of the suspension. The rate and extent of absorption of cefdinir decrease, although not clinically significantly, when the drug is taken with a high-fat meal. Thus, cefdinir may be taken without regard to food.

The mean volume of distribution of cefdnir is 1.56–2.09 L/kg in adults and 0.67 L/kg in paediatric patients. The drug is 60–73% plasma protein bound. Cefdinir is widely distributed and achieves clinically relevant concentrations in bronchial mucosa, epithelial lining fluid, tonsillar tissue, sinus tissue, skin blister fluid and middle ear fluid.

Cefdinir is not metabolised to an appreciable extent and is eliminated via the kidneys. After single oral doses of 300 or 600mg, renal clearance was ≈2 mL/min/kg and apparent oral clearance values were 11.6 and 15.5 mL/min/kg. The plasma elimination half-life of cefdinir is 1.5–1.7 hours in adults and 1.2–1.5 hours in healthy infants and children.

The pharmacokinetics of cefdinir are altered in patients with renal impairment and dosage modification is required for those with a creatinine clearance (CL_{CR}) of <30 mL/min (<1.8 L/h).

When coadministered with aluminium/magnesium-containing antacids or iron supplements, the gastrointestinal absorption of cefdinir is impaired. Thus, the manufacturer recommends that cefdinir is taken ≥2 hours before or after these agents. Like other β-lactam antibacterials, cefdinir interacts with probenecid and marked increases in systemic exposure to cefdinir occur when the two drugs are coadministered. Reddish stools, resulting from the formation of a nonabsorbable complex between cefdinir (or its breakdown products) and iron, have been reported in some patients.

Therapeutic Efficacy

Oral cefdinir 300mg twice daily or 600mg once daily in adults and adolescents, or 14 mg/kg/day in one or two divided daily doses in paediatric patients, administered for 5 or 10 days, has shown good clinical and bacteriological efficacy at least equivalent to that of oral comparator agents in randomised, controlled trials conducted in patients with a wide range of infections. In most trials, patients had documented pathogens at baseline.

Adults and Adolescents: At test-of-cure (TOC) visits, cefdinir 300mg twice daily or 600mg once daily demonstrated clinical and bacteriological efficacy equivalent to that of cefprozil (bacteriological only), loracarbef and cefuroxime axetil in adults and adolescents with acute bacterial exacerbations of chronic bronchitis (ABECB). In one trial, cefdinir 300mg twice daily for 5 days produced a higher clinical cure rate (80.3%) than cefprozil 500mg twice daily for 10 days (71.9%): clinical cure rates were not equivalent based on 95% confidence inter-

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vals. At long-term follow-up (up to 42 days post-treatment), clinical cure and bacteriological eradication rates remained high (>80% for cefdinir and the comparator groups).

In a single trial in adults and adolescents with community-acquired pneumonia (CAP), cefdinir 300mg twice daily for 10 days was equivalent to cefaclor 500mg three times daily for 10 days in terms of both clinical and bacteriological efficacy at the TOC assessments. Clinical success rates with cefdinir and cefaclor were 89% and 86%, respectively, and bacteriological eradication rates were >90% for both groups.

Cefdinir 300mg twice daily or 600mg once daily for 10 days showed clinical and bacteriological efficacy equivalent to that of standard regimens of amoxicillin/clavulanic acid in trials conducted in adults and adolescents with acute bacterial rhinosinusitis. Clinical responses (clinical cure, or cure plus improvement) were achieved in ≥87% of patients at the TOC visits.

Adults and adolescents with streptococcal pharyngitis/tonsillitis were also successfully treated with cefdinir 300mg twice daily (for 5 or 10 days) or 600mg once daily for 10 days. Cefdinir was at least as effective as penicillin V (250mg four times daily for 10 days). High rates of eradication of *S. pyogenes* were reported with cefdinir (88.5–91.7%) and both eradication rates and clinical cure rates with 10-day courses of cefdinir were significantly ($p \leq 0.02$) higher than rates achieved with penicillin V at the TOC assessment. Cefdinir 300mg twice daily for 10 days was also an effective treatment for adults and adolescents with skin and skin structure infections and showed clinical and bacteriological efficacy similar to that of cefalexin.

Paediatric Patients: In the treatment of paediatric patients with acute otitis media, cefdinir, administered as a suspension, at a dosage of 7 mg/kg twice daily for 5 or 10 days or 14 mg/kg once daily for 10 days, showed similar clinical efficacy to that of standard regimens of amoxicillin/clavulanic acid or cefprozil.

Cefdinir was also an effective treatment for paediatric patients with streptococcal pharyngitis/tonsillitis. In two comparative trials, rates of eradication of *S. pyogenes* in patients treated with cefdinir 14 mg/kg/day for 5 or 10 days were significantly ($p < 0.001$) higher (≥90%) than in recipients of 10-day courses of penicillin V 40 mg/kg/day (≈70%). In addition, clinical cure rates with 10-day courses of cefdinir (≥96%) were significantly ($p = 0.001$) higher than the clinical cure rate (86.3%) in the penicillin V treatment group. Cefdinir 7 mg/kg twice daily for 10 days showed good clinical and bacteriological efficacy, equivalent to that of cefalexin, in paediatric patients with uncomplicated skin and skin structure infections.

Tolerability

Cefdinir was generally well tolerated by adults, adolescents and paediatric patients in randomised clinical trials that enrolled patients with respiratory tract or skin infections. Most reported adverse events were minor and self-limiting and discontinuation rates due to adverse events were low (1–6%). As with most antibacterials, pseudomembranous colitis has occasionally been reported in recipients of cefdinir. Overgrowth of *Clostridium difficile* should therefore be considered in patients presenting with diarrhoea during treatment.

Adults and Adolescents: According to pooled data from US clinical trials, diarrhoea (incidence 15%) was the most common adverse event in adults and

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adolescents receiving cefdinir capsules at therapeutic dosages. Similarly, in individual randomised trials, diarrhoea (usually mild) was the most common event (incidence 7.8–33%) in patients treated with cefdinir 300mg twice daily or 600mg once daily. Nausea and headache were the other most frequently reported events (incidence ≤3%) in the pooled analysis.

The incidence of most adverse events (e.g. nausea and headache) with cefdinir is similar to that reported for cefaclor, cefprozil, cefuroxime axetil, loracarbef, penicillin V and amoxicillin/clavulanic acid. However, in comparative trials, the incidence of diarrhoea was significantly (all $p \leq 0.04$) higher in recipients of cefdinir than in those treated with cefaclor, cefprozil, cefalexin, loracarbef or penicillin V. The overall incidence of adverse events in cefdinir treatment groups was also significantly ($p \leq 0.008$) higher than in recipients of cefaclor, loracarbef or cefalexin. However, discontinuation rates due to adverse events were similar for cefdinir and the comparator groups in all but two trials in which discontinuation rates were significantly lower ($p \leq 0.02$) with cefdinir than with amoxicillin/clavulanic acid.

Paediatric Patients: In a pooled analysis of US clinical trials, and in individual randomised trials, diarrhoea (incidence 8% in the pooled analysis, 2.9–15.9% in the individual trials) was the most common adverse event in paediatric patients receiving cefdinir suspension at therapeutic dosages. Other adverse events included rash and vomiting (incidence ≤3%). In comparative trials, the incidence of adverse events with cefdinir suspension was similar to that reported for cefprozil, penicillin V or cefalexin suspensions. In addition, the incidence of diarrhoea with cefdinir was broadly similar to that reported for cefprozil, penicillin V suspension or amoxicillin/clavulanic acid suspensions. The overall incidence of adverse events with amoxicillin/clavulanic acid was significantly higher than in recipients of cefdinir 14 mg/kg once daily (26.2% vs 16.7%; $p = 0.01$) in one comparative trial in patients with acute otitis media. In a similar trial, diarrhoea occurred significantly ($p < 0.001$) more frequently with amoxicillin/clavulanic acid (35%) than with cefdinir 7 mg/kg twice daily (13%) or 14 mg/kg once daily (10%). Rates of treatment discontinuation due to adverse events were similar in recipients of cefdinir, cefprozil or penicillin V. Discontinuation rates in cefdinir recipients were similar to or lower than rates reported for patients treated with amoxicillin/clavulanic acid.

Dosage and Administration

Cefdinir is approved in the US for the treatment of adults, adolescents and paediatric patients with mild-to-moderate bacterial infections caused by susceptible strains of specific pathogens. The drug is available as capsule and strawberry-flavoured suspension formulations and can be administered without regard to food. When given concomitantly, antacids containing magnesium/aluminium, and iron supplements, reduce the the absorption of cefdinir. These agents should be taken ≥2 hours before or after administration of cefdinir.

In adults and adolescents, cefdinir is approved for the treatment of CAP, ABECB, acute maxillary rhinosinusitis, pharyngitis/tonsillitis, and uncomplicated skin and skin structure infections. Approved dosages are 300mg every 12 hours for 10 days (for CAP, uncomplicated skin and skin structure infections, and acute maxillary rhinosinusitis), 300mg every 12 hours for 5 or 10 days (ABECB and pharyngitis/tonsillitis) and 600mg every 24 hours for 10 days (ABECB, acute

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maxillary rhinosinusitis and pharyngitis/tonsillitis). Dosage modification is required for patients with renal impairment (CL_{CR} <30 mL/min; <1.8 L/h); the dosage should be reduced to 300mg once daily.

In paediatric patients aged 6 months to 12 years, cefdinir is approved for the treatment of acute otitis media, acute maxillary rhinosinusitis, pharyngitis/tonsillitis and uncomplicated skin and skin structure infections: approved dosages are 7 mg/kg every 12 hours for 5–10 days or 14 mg/kg every 24 hours for 10 days (acute otitis media, pharyngitis/tonsillitis), 7 mg/kg every 12 hours or 14 mg/kg every 24 hours for 10 days (acute maxillary rhinosinusitis), and 7 mg/kg every 12 hours for 10 days (skin and skin structure infections). In paediatric patients with renal impairment (CL_{CR} <30 mL/min/1.73m^2), the recommended dosage of cefdinir is 7 mg/kg (to a maximum of 300mg) once daily.

1. Introduction

Cefdinir (Omnicef®)[1] [figure 1] is an oral expanded-spectrum, third-generation cephalosporin with improved stability against many common β-lactamases, a distinct advantage over first and second generation cephalosporins in the treatment of β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella catarrhalis*. Cefdinir was approved by the US FDA in December 1997 for the treatment of various mild-to-moderate infections caused by susceptible strains of specific pathogens.[1,2] Cefdinir is also available in Japan and China.

In the US, cefdinir is approved for the treatment of adults or adolescents with community-acquired pneumonia (CAP), acute bacterial exacerbations of chronic bronchitis (ABECB), acute maxillary rhinosinusitis, streptococcal pharyngitis/tonsillitis, and uncomplicated skin and skin structure infections (see section 6).[2] In addition, it is approved for the treatment of acute otitis media, streptococcal pharyngitis/tonsillitis, acute maxillary rhinosinusitis, and uncomplicated skin and skin structure infections in paediatric patients.[2] This review summarises data on the antibacterial activity and clinical pharmacology of cefdinir, and focuses on its efficacy in the treatment of adults, adolescents and paediatric patients with the aforementioned infections.

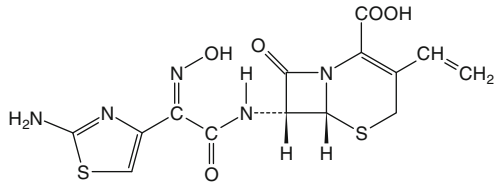

Fig. 1. Chemical structure of cefdinir.

2. Antibacterial Activity

This section provides a summary of data on the *in vitro* activity of cefdinir against clinically relevant pathogens. Information on the *in vivo* efficacy of the drug in animal models of infection is also briefly discussed.

2.1 *In Vitro* Activity

Cefdinir is approved in the US for the treatment of infections caused by susceptible strains of the following microorganisms: *Streptococcus pneumoniae* (penicillin-susceptible strains), *S. pyogenes*, *Staphylococcus aureus* (methicillin-susceptible strains), *H. influenzae*, *H. parainfluenzae* and *M. catarrhalis*.[2] This section focuses on the *in vitro* activity of cefdinir against these microorganisms. Data on its activity against clinical isolates of penicillin-intermediate and -resistant strains of *S. pneumoniae* are also briefly summarised because of the increase in penicillin resistance rates among clinical isolates of pneumococci worldwide.[3,4]

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

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As bacterial susceptibility patterns change over time, most of the reviewed data are compiled from studies published since 1995. However, results of older studies are included when needed to complete the *in vitro* antibacterial profile of the drug. Data on the *in vitro* activity of cefdinir against clinically relevant Gram-positive and -negative bacteria are presented in table I.

For comparison, information is also provided on the antibacterial activity of cefuroxime (a second-generation cephalosporin) and cefpodoxime (a third-generation cephalosporin). *In vitro* activity (table I) was assessed in terms of minimum concentrations required to inhibit the growth of 50% (MIC_{50}) or 90% (MIC_{90}) of bacterial strains. Current US National Committee for Clinical Laboratory Standards (NCCLS) interpretive breakpoint concentrations for cefdinir against relevant microorganisms are provided in table II.[33] Owing to the lack of data on resistant strains of *H. influenzae*, breakpoint values are available for susceptible strains only (table II).[2]

2.1.1 Gram-Positive Aerobic Bacteria

Cefdinir has shown consistently good *in vitro* activity against penicillin-susceptible strains of *S. pneumoniae* (MIC_{90} range 0.06–0.5 mg/L) in numerous studies conducted in the US, Europe, Japan and other countries (table I).[6,11,12,15,16,18,21-24,26,29,31] Comparisons of results of studies conducted before 1995[35-44] with more recent data (table I) indicate that the activity of cefdinir against penicillin-susceptible strains of pneumococci has not changed appreciably during the last decade. Like many other β-lactam antibacterial agents, cefdinir is less active against penicillin-intermediate and -resistant strains of *S. pneumoniae*, with MIC_{90} values ranging from 1 to 16 mg/L[16,18,21-26,29,31] and from >2 to 32 mg/L,[6,12,14-16,18,21-26,29,31] respectively (table I). The *in vitro* activity of cefdinir against penicillin-susceptible strains of *S. pneumoniae* is similar to that of both cefpodoxime and cefuroxime (100% susceptibility for all tested strains: table I).

In common with cefpodoxime and cefuroxime, cefdinir is very active against *S. pyogenes* and is a good candidate for use in the treatment of patients with upper respiratory tract infections caused by this pathogen (see sections 4.1.4 and 4.2.2). Across a number of studies conducted in various countries, including the US, Europe and Japan, *S. pyogenes* strains were highly susceptible to cefdinir; MIC_{90} values ranged from 0.012 to ≤0.03 mg/L and all tested strains were susceptible to the drug (table I).[6,9,11-13,15,19,20,31]

Cefdinir is also active against methicillin-susceptible strains of *S. aureus*, including β-lactamase-producing strains. Mean cefdinir MIC_{90} values (range 0.25–1 mg/L[6,7,9-15,29,31]) tended to be lower than those reported for cefpodoxime (2–6 mg/L[6,7,12,13,29,31]) in studies published since 1995 (table I). This observation is consistent with the results of an earlier European study (n = 40 strains) in which mean MIC_{90} values of 0.5 and 4 mg/L were reported for cefdinir and cefpodoxime.[35] In a review of the *in vitro* antibacterial activity of oral cephalosporins,[45] cefdinir was reported to be more active against oxacillin-/methicillin-susceptible *S. aureus* than cephalosporin comparators, including cefuroxime, cefpodoxime, cefalexin and cefaclor.

Cefdinir showed good activity against various pathogens isolated from patients with community-acquired skin and soft tissue infections in a recent North American multicentre (34 medical centres) study reported as an abstract.[46] Most isolates were Gram positive (e.g. oxacillin-susceptible [OS] *S. aureus* [n = 243], OS coagulase-negative staphylococci [21], *S. agalactiae* [28] and *S. pyogenes* [57]). Overall, the activity of cefdinir was comparable or superior to that of cefaclor, cefprozil, cefuroxime and cefpodoxime. [46] Like other β-lactam agents, cefdinir is inactive against methicillin-resistant staphylococci.

2.1.2 Gram-Negative Aerobic Bacteria

Cefdinir exhibited good activity against clinical isolates of *H. influenzae,* one of the most common respiratory tract pathogens, with MIC_{90} values in the majority of studies ranging from 0.5 to 1 mg/L.[5,6,13,16-19,23,28-30,32] Cefuroxime and cefpodoxime were also active against *H. influenzae*, including β-lactamase producers (table I).

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Table I. *In vitro* activity of cefdinir, cefuroxime and cefpodoxime against clinically relevant Gram-positive and -negative bacteria. Data are derived from *in vitro* studies published since 1995 evaluating clinical isolates collected from the US, Europe, Japan and other countries. Susceptibility testing was usually performed using broth or agar dilution techniques. Data are presented as ranges of MIC_{50}, MIC_{90} (means) and % susceptibility values

Organism	n[a]	Cefdinir[5-32]			Cefuroxime[5,8,9,16-19,21,23,24,27-30,32]			Cefpodoxime[6,7,12,13,17,21-24,26,28-31]			References
		MIC_{50} (mg/L)	MIC_{90} (mg/L)	S (%)[b]	MIC_{50} (mg/L)	MIC_{90} (mg/L)	S (%)[b]	MIC_{50} (mg/L)	MIC_{90} (mg/L)	S (%)[b]	
Gram-positive organisms											
Streptococcus pneumoniae											
PS	3040	0.031–0.25	0.06–0.5[c]	100	≤0.016–0.06	0.03–0.125	100	<0.015–0.06	≤0.03–1	100	6,11,12,14-16,18,21-24,26,29,31
PI	940	0.12–8	1–16	16.7–78.6	0.5–1	1–8	20–82.1	0.12–2	1–2	19.4	16,18,21-26,29,31
PR	1204	4–8[d]	>2.0–32.0	0	4–8	4–16	0	2–4[e]	1.56–8	0	6,12,14-16,18,21-26,29,31
S. pyogenes	300	0.008–≤0.03	0.012–≤0.03	100	0.008–0.016	0.016–0.06	100	0.016–0.032	0.016–0.032	100	6,9,11-13,15,19,20,31
Staphylococcus aureus	634	0.12–0.75[f]	0.25–1.0[g]	100	1–1.6	1–3.1	NA	2–4	2–6	0	6,7,9-15,29,31
Gram-negative organisms											
Haemophilus influenzae[h]	17 224	0.25–1	0.39–2[i]	87–100[j]	0.5–1.6	1–8	93.8–100	0.03–0.125	0.06–1	90.5–100	5,6,8,11-19,23,27-32
H. parainfluenzae[h]	84	0.5	1	100	1	4	100	NA			19
Moraxella catarrhalis[h]	5385	0.05–0.5	0.12–1	100	0.25–1	0.5–2	98.7–100	0.12–2	0.12–2	32.1–100	5,6,8,11-19,28-32

a Total number of clinical isolates used to determine the activity of cefdinir.

b Percentage of organisms that were classed as susceptible (S) according to the breakpoints used by the study investigators (e.g. breakpoints of the US National Committee for Clinical Laboratory Standards). Not reported in all studies.

c Excluding a single outlier value of 4 mg/L (n = 66).[14]

d Excluding two outlier values of 0.39 mg/L (n = 21)[12] and 1.56 mg/L (n = 28).[15]

e Excluding a single outlier value of 0.39 mg/L (n = 21).[12]

f Excluding a single outlier value of 1.6 mg/L (n = 53).[8]

g Excluding a single outlier value of 3.1 mg/L (n = 53).[8]

h Including both β-lactamase-positive and -negative strains.

i Excluding a single outlier value of 4 mg/L (n = 74).[31]

j Excluding a single outlier value of 73%.[31]

$MIC_{50/90}$ = mean minimum inhibitory concentrations required to inhibit the growth of 50% or 90% of bacterial strains; **NA** = not available; **PI** = penicillin-intermediate (MIC 0.12–1 mg/L); **PR** = penicillin-resistant (MIC ≥2 mg/L); **PS** = penicillin-susceptible (MIC ≤0.06 mg/L).

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Table II. Interpretive categories of minimum inhibitory concentration (MIC) breakpoints for cefdinir as recommended by the US National Committee for Clinical Laboratory Standards[2,33]

	Breakpoint concentration (mg/L)		
	susceptible	intermediate	resistant
Organisms other than *Haemophilus* spp. and *Streptococcus* spp.[a]	≤1	2	≥4
S. pneumoniae	≤0.5	1	≥2
Haemophilus spp.	≤1[b]		

a *S. pneumoniae* that are susceptible to penicillin (MIC ≤0.06 mg/L) or other streptococci that are susceptible to penicillin (MIC ≤0.12 mg/L) are considered susceptible to cefdinir.

b Applicable only to broth microdilution tests using *Haemophilus* Test Medium.[2,34]

Importantly, cefdinir showed similar activity against β-lactam-positive and -negative strains of *H. influenzae* in each of the studies that differentiated strains on the basis of β-lactamase production (figure 2).[16,23,28-31]

Of note, in the PROTEKT study, a recent large international surveillance study that examined the susceptibility of *H. influenzae* to various antibacterial agents, cefdinir was very active against β-lactamase-positive (n = 489) and -negative strains (2459) [figure 2].[28] Furthermore, ≈100% of tested strains in each group were susceptible to the drug at the NCCLS-approved breakpoint.[28] Geographical variation of the activity of cefdinir against *H. influenzae* was evident in a smaller study that tested clinical isolates (n = 63 β-lactamase-negative; 11 β-lactamase-positive) from children aged <15 years with bacterial respiratory tract infections in Japan (figure 2).[31] An unusually high MIC_{90} of 4 mg/L was reported for both β-lactamase-positive and β-lactamase-negative strains[31] (figure 2). This study may have included a few isolates with penicillin-binding protein (PBP) mutations, which are more common in Japan, and the test method may have differed from that in the other studies.

Cefdinir displayed good activity against both β-lactamase-positive and -negative strains of *H. parainfluenzae* in a study conducted in Italy (table I).[19]

Across numerous studies conducted in various geographic locations, cefdinir exhibited very good activity against both β-lactamase-positive and -negative strains of *M. catarrhalis* (table I).[5,6,8,11-19,28-32] In the studies that reported susceptibility data, 100% of strains were susceptible to cefdinir; mean MIC_{90} values ranged from 0.12 to 1 mg/L (table I). The activity of cefdinir against β-lactamase-positive strains of *M. catarrhalis*, as measured by MIC_{90} and MIC_{50} values, was broadly similar to that against β-lactamase-negative strains in two studies that differentiated between strains.[19,28] In the largest of these, the PROTEKT surveillance study,[28] mean MIC_{90} values against 1071 β-lactamase-positive strains and 60 β-lactamase-negative strains were 0.25 and 0.12 mg/L.

Cefdinir showed good activity against various pathogens, most of which were Gram-negative (e.g. *Escherichia coli* [n = 205], *Klebsiella* spp. [38], *Proteus mirabilis* [20]) collected from patients with community-acquired urinary tract infections in 23 medical centres in North America in 2003.[47] Overall, the activity of cefdinir was comparable or superior to that of cefuroxime, cefprozil and cefpodoxime. Resistance to cefdinir was rare and was identified only among *E. coli* (incidence 1.5%) and *Klebsiella* spp. (2.6%).[47]

2.2 β-Lactamase Stability

The most common mechanism of bacterial resistance to β-lactam antibacterials is mediated via the production of β-lactamases. These bacterial enzymes, which can be plasmid- or chromosome-mediated, inactivate many β-lactam antibacterials by hydrolysing the amide bonds of the β-lactam ring.[48]

Emergence of resistance among *H. influenzae,* primarily mediated via the production of TEM-1 type β-lactamases, became evident in the early 1970s and has increased over time.[28,49,50] Indeed, about one-third of *H. influenzae* strains in the US were reported to be β-lactamase producers in recent surveillance studies.[28,50] Similarly, β-lactamase-producing *M. catarrhalis* strains have become more prevalent during the last 30 years such that currently >90% of strains worldwide are β-lactamase producers.[28,49,51] The β-lactamases produced by *M. catarrhalis* have been characterised as BRO-1, BRO-

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2[28,51] and BRO-3,[28] and are chromosomal. In *in vitro* investigations, cefdinir showed very good activity against β-lactamase-producing strains of *M. catarrhalis*, including those characterised as producing BRO-1 and BRO-2,[28] indicating that the drug is resistant to hydrolysis by these bacterial enzymes.

Cefdinir is stable to hydrolysis by many of the common plasmid-mediated β-lactamases (e.g. TEM-1, TEM-2, TEM-6, TEM-7, TEM-9, TEM-10, HMS-1, CAZ-2, SHV-1, OXA-1, OXA-2, OXA-3 and P99 type 1a).[36,38,39,52-55] Pathogens with β-lactamase-mediated resistance to penicillin and first- or second-generation cephalosporins may therefore be susceptible to cefdinir.[2] Overall, the stability of cefdinir to hydrolysis by plasmid-mediated β-lactamases appears to be greater than that of cefuroxime.[37]

However, cefdinir is susceptible to hydrolysis by a number of plasmid-mediated extended-spectrum β-lactamases (e.g. TEM-3, TEM-4, TEM-5, PSE-2, P99 type 1c, SHV-2, SHV-3, SHV-4, SHV-5, MEN-1, K-1, CARB-1, CARB-2, CARB-3 and OXA-4) and chromosome-mediated β-lactamases (inducible cephalosporinases) present in some Enterobacteriaceae species (reviewed by Appelbaum[37] and Guay[1]).

2.3 Bactericidal Activity

Like other cephalosporins, cefdinir binds with high affinity to PBPs, thereby inhibiting cell wall synthesis and inducing thickening of the bacterial cell wall. This leads to lysis and death of susceptible bacteria.[56] The minimum concentration of an antibacterial required to kill 99.9% of an initial inoculum of bacteria is termed the minimum bactericidal concentration (MBC). In studies evaluating the bac-

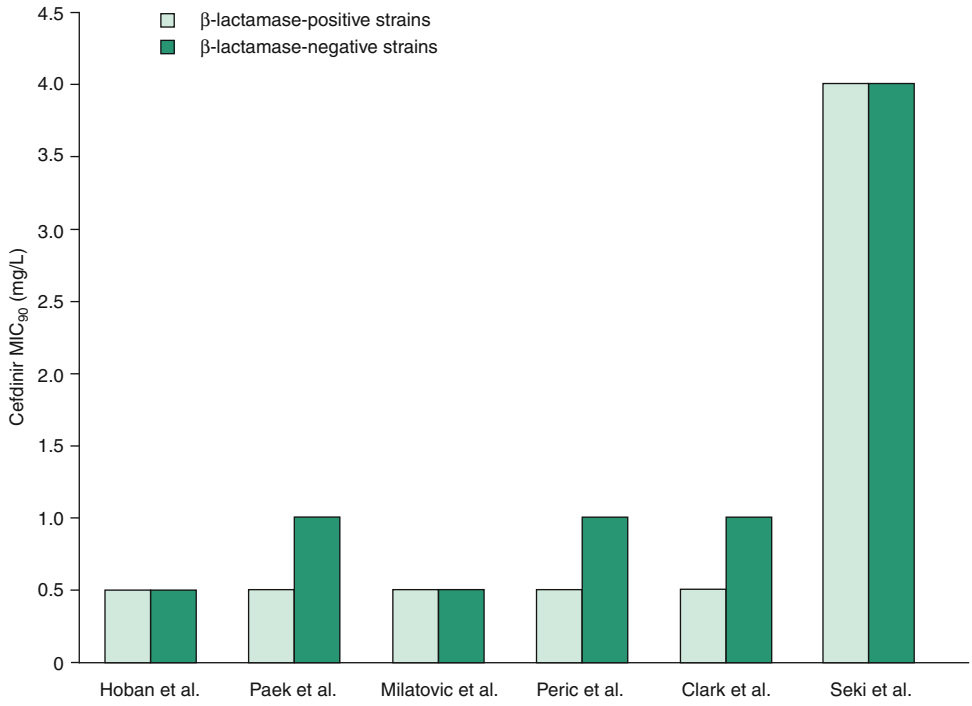

Fig. 2. *In vitro* activity of cefdinir against β-lactamase-positive and -negative strains of *Haemophilus influenzae*.[16,23,28-31] Minimum concentrations of cefdinir inhibiting 90% (MIC_{90}) of strains of β-lactamase-positive and -negative strains of *H. influenzae* isolated from multiple countries (e.g. the US, Canada, South America, Hungary, Poland, Japan, Australia [the PROTEKT study],[28] the US,[23,29] Europe,[30] Korea[16] and Japan[31]).

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tericidal activity of cefdinir against various common Gram-positive and -negative organisms, MBCs were either the same or only one dilution greater than corresponding MICs (reviewed by Appelbaum[37]).

Results of killing kinetic studies have shown that cefdinir is rapidly bactericidal at concentrations of two to four times the MIC.[36-38,57,58] The bactericidal activity of cefdinir was not affected by the presence of human serum or urine in several *in vitro* investigations.[38,39,59,60] An inoculum effect has been observed in *in vitro* investigations of cefdinir, although this effect was generally minor for most species of bacteria (reviewed by Guay[61]).

2.4 *In Vivo* Activity

Although *in vitro* data provide an indication of the activity of cephalosporins against specific pathogens, this information does not necessarily correlate with clinical efficacy because of the interaction between pharmacodynamic and pharmacokinetic parameters (e.g. the time that plasma drug concentrations are above the MIC against a particular pathogen)[62,63] [see reviews by Nicolau[64] and Novelli et al.[65]]. Thus, information on the efficacy of antibacterials against infections caused by specific pathogens in animal models of infection is of additional interest.

The efficacy of cefdinir against various infections in animals has been documented in several studies conducted in Japan.[6,9,12,66-68] Cefdinir showed good efficacy in the treatment of experimental pneumonia caused by *S. pneumoniae* (penicillin-susceptible strains)[9,66] or *H. influenzae*[67,68] in mice. Murine subcutaneous abscesses induced by *S. aureus* also responded to cefdinir, as evidenced by reductions in the number of recoverable viable bacteria in the skin at sites of infection.[67]

3. Pharmacokinetic Properties

The pharmacokinetic properties of orally administered cefdinir have been investigated in healthy adults, paediatric patients and individuals with renal impairment. Most data in this section are from single-dose studies and relate to the pharmacokinetic profile of cefdinir in adult recipients of the capsule formulation. A summary of available data on the pharmacokinetics of cefdinir, administered as a suspension, in paediatric patients is also included. Neither race nor gender were found to affect the pharmacokinetics of cefdinir in a meta-analysis of data from 217 recipients of the drug (study population aged 6 months to 12 years).[2]

3.1 Absorption

Absorption parameters of cefdinir after single doses of the capsule (in adults) or suspension (in paediatric patients) are presented in table III.

In adults, cefdinir is absorbed rapidly from the capsule formulation.[1] Mean maximum plasma concentrations (C_{max}) of 1.6 and 2.87 mg/L after single doses of 300 and 600mg, respectively, occurred at a mean time (t_{max}) of ≈3 hours after administration (table III).[2] C_{max} was attained in a shorter time (t_{max} ≈2 hours) in paediatric patients given the suspension formulation;[2,69] Mean C_{max} values of 2.3 and 3.86 mg/L were reported after single doses of 7 and 14 mg/kg, respectively (table III).[2] Cefdinir does not accumulate in the plasma of individuals with normal renal function receiving therapeutic dosages of the drug.[2]

In 16 healthy male adult volunteers who participated in a randomised single-dose crossover study, cefdinir had a linear pharmacokinetic profile over a 200–400mg dose range.[1,70] After administration of a higher dose (600mg), the drug showed nonlinear pharmacokinetics probably as a result of absorption saturation and tubular secretion in the kidneys.[1,70] After doses of 200, 300, 400 and 600mg, mean C_{max} values were 1.0, 1.55, 2.15 and 2.35 mg/L, respec-

Table III. Absorption parameters (mean values) of cefdinir after single oral doses of the capsule (adults) or suspension (paediatric patients aged 6 months to 12 years)[2]

Parameter	Adults		Paediatric patients	
	300mg	600mg	7 mg/kg	14 mg/kg
C_{max} (mg/L)	1.6	2.87	2.3	3.86
t_{max} (h)	2.9	3.0	2.2	1.8
AUC (mg • h/L)	7.05	11.1	8.31	13.4

AUC = area under the plasma concentration-time curve; $\mathbf{C_{max}}$ = maximum plasma concentration; $\mathbf{t_{max}}$ = time to reach C_{max}.

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tively, and mean area under the plasma concentration-time curve (AUC) [from zero to infinity] values were 4.08, 6.53, 8.83 and 9.84 mg • h/L.

The bioavailability of cefdinir has been estimated to be 21% (300mg capsule) and 16% (600mg capsule).[2] The estimated absolute bioavailability of cefdinir from the suspension formulation is 25%.[2]

Compared with absorption parameters of cefdinir in fasted adults, both the rate and extent of absorption of the drug decrease when it is taken with a high-fat meal.[2,71] However, neither parameter is affected to a clinically significant extent and so cefdinir can be administered without regard to food (see section 6).

3.2 Distribution

The mean volume of distribution (Vd) of cefdinir ranged from 1.56–2.09 L/kg after single doses of 200–600mg in adults.[70] Vd values of 0.35 L/kg in adults and 0.67 L/kg in paediatric patients (age range 6 months to 12 years) have also been reported.[2] Cefdinir is 60–73% bound to plasma proteins; the extent of plasma protein binding is independent of plasma cefdinir concentrations.[1,2,72] The drug was found to bind to bovine serum albumin in isolated perfused rat kidney.[73]

Cefdinir is widely distributed and shows good penetration into bronchial muscosa and epithelial lining fluid (but not alveolar macrophages), tonsillar tissue, sinus tissue, skin blister fluid and middle ear fluid.[2,70,74] About 4 hours after administration of single 300 or 600mg doses to 16 healthy adult volunteers, median cefdinir concentrations in bronchial mucosa were 0.78 and 1.14 mg/L, respectively; median concentrations in epithelial lining fluid were 0.29 and 0.49 mg/L.[74] The extent of penetration of cefdinir into bronchial mucosa after both doses was 31–41%.

3.3 Elimination

Cefdinir is not appreciably metabolised in adults and is predominantly eliminated via the kidneys as unchanged drug.[2] Data on the elimination of cefdinir in paediatric patients are limited at present. In adults receiving single cefdinir doses of 300 or 600mg, ≈18%[2,70] and 12–13%,[2,70] respectively, of the total dose was recovered as unchanged drug in the urine. A smaller proportion (mean range 2.7–12.7%) of an administered dose (dose and number of study participants not reported) was eliminated unchanged in children (data reviewed by Guay[75]). Renal clearance was ≈2 mL/min/kg,[2,70] and apparent oral clearance values were 11.6 and 15.5 mL/min/kg[2] after single oral doses of 300 and 600mg, respectively, in adults with normal renal function. The nonlinear renal clearance of the drug after a single 600mg dose may be due to a rate-limited renal elimination process (e.g. active tubular secretion).[70] An anionic secretory pathway was the main mechanism of renal excretion of cefdinir in an isolated perfused rat kidney experiment.[73] Notably, the clearance of the drug is reduced in individuals with renal impairment (see sections 3.4 and 6). Cefdinir has a plasma elimination half-life ($t_{1/2}$) of 1.5–1.7 hours in adults.[2,70] In a nonblind single-dose study, the $t_{1/2}$ ranged from 1.2 to 1.5 hours in healthy infants and children (n = 24) aged 6 months to 12 years who received single doses of 7 or 14 mg/kg.[69]

3.4 Special Populations

The pharmacokinetics of cefdinir are altered in patients with renal impairment and dosage modification may be required, depending of the severity of impairment (see section 6).[2] The rate of elimination, apparent oral clearance and renal clearance of cefdinir each decreased (approximately in proportion with decreasing creatinine clearance [CL_{CR}]) in 21 adults with varying degrees of renal function, resulting in higher plasma cefdinir concentrations and prolonged systemic exposure to the drug.[2]

In patients with marked renal impairment (CL_{CR} <30 mL/min; 1.8 L/h), C_{max}, $t_{1/2}$ and AUC increased by approximately 2-, 5- and 6-fold, respectively, compared with values in individuals with normal renal function.[2] Dosage reduction is therefore recommended for this patient group (see section 6).[2]

However, although cefdinir C_{max} and $t_{1/2}$ values were ≈2-fold higher and AUC values were approximately 3-fold higher in patients with a CL_{CR} of

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Table IV. Summary of interactions between cefdinir and concomitantly administered drugs in adult volunteers

Drug	Dose of cefdinir (mg)	Effect on cefdinir pharmacokinetic parameter[a]
Aluminium/magnesium-containing antacid[b] (30mL)	300	↓ C_{max} and ↓ AUC (by 40% for both); ↑ t_{max} (by 1h)[2]
Probenecid 1g	300	↑ AUC (by 2-fold); ↑ C_{max} (by 54%); ↑ $t_{½}$ (by 50%)[2]
Elemental iron 210mg[c]	200	↓ $AUC_{0–12h}$ (by 92%)[76]
Elemental iron 60mg[c]	300	↓ AUC (by 80%)[2]

a Compared with parameters in recipients of cefdinir alone.

b Maalox®.

c Administered as ferrous sulphate.

AUC = area under the plasma concentration-time curve; **$AUC_{0–12h}$** = AUC from 0 to 12 hours; **C_{max}** = maximum plasma concentration; **$t_{½}$** = apparent elimination half life; **t_{max}** = time to C_{max}; ↓ indicates decrease; ↑ indicates increase.

30–60 mL/min (1.8–3.6 L/h) than in patients with normal renal function, dosage modification is not required for this population.[2]

Cefdinir is removed from the body by haemodialysis.[2,72] Fractional removal of cefdinir by haemodialysis (4-hour session) was 61% and mean clearance was 75.7 mL/min (4.54 L/h) in six patients.[72]

Systemic exposure to cefdinir in the elderly is higher than in younger individuals because of age-related declining renal function and, as a consequence, reduced renal clearance of the drug.[2] Nevertheless, dosage modification is not required for this population unless CL_{CR} is <30 mL/min (<1.8 L/h) [see section 6]. Mean C_{max} and AUC values were, respectively, 44% and 86% higher in 16 elderly individuals than in a comparator group of 16 younger individuals.[2] The apparent Vd of cefdinir was also reduced in the elderly group, whereas the $t_{½}$ (2.2 hours) was broadly similar to that in younger individuals (1.8 hours).[2]

The pharmacokinetics of cefdinir have not been studied in patients with hepatic impairment because the drug does not undergo appreciable metabolism in the liver and hepatic insufficiency is not expected to alter its pharmacokinetic profile.

3.5 Drug Interactions

Cefdinir has a favourable drug interaction profile, interacting with few concomitantly administered drugs, as shown in table IV.[2,76] There are no published reports of cefdinir affecting the pharmacokinetics of coadministered agents.

Both the rate and extent of absorption of cefdinir are substantially reduced when it is coadministered with an aluminium/magnesium-containing antacid suspension (table IV); an interval of ≥2 hours between administration of cefdinir and aluminium/magnesium-containing antacids is recommended by the manufacturer (see section 6).[2] Like other β-lactam antibacterials, cefdinir interacts with probenecid. Marked increases in systemic exposure to cefdinir occur when the two drugs are coadministered (table IV) because probenecid inhibits the renal excretion of cefdinir.[2]

Systemic exposure to cefdinir decreased by 80%[2] and 92%[76] when it was coadministered with ferrous sulphate preparations (table IV). It has been suggested that this interaction is due to the formation of a cefdinir/elemental iron chelation complex, which impairs the gastrointestinal absorption of cefdinir.[76] The manufacturer recommends that cefdinir is taken ≥2 hours before or after iron supplements (section 6).[2] However, cefdinir may be administered to infants (aged ≥6 months) receiving infant formula fortified with iron.[2] The pharmacokinetics of cefdinir were not significantly affected after administration of cefdinir suspension 7 mg/kg with 2.2mg elemental iron/6oz iron-fortified infant formula.[2,77] Reddish stools have been reported in patients receiving cefdinir, most of whom were also taking iron-containing preparations.[2] This has been attributed to an nonabsorbable complex formed by cefdinir (or its breakdown products) and iron.[2]

Both captopril and quinapril (and/or their metabolites) had a marked effect on the disposition of cefdinir (increased systemic exposure, increased Vd, decreased elimination) in rats.[78] The investigators attributed this interaction to probable competi-

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tion for plasma protein binding sites and competition at the tubular anionic carrier level.[78]

4. Therapeutic Efficacy

The efficacy of oral cefdinir has been investigated in numerous randomised, double-blind or single-blind, active-controlled, multicentre trials. This section focuses on large fully published comparative trials that enrolled either adults and adolescents or paediatric patients with various types of bacterial infections. At study entry, most trial participants had infections that were categorised as mild or moderate in severity. Assessments of clinical efficacy (usually 'clinical cure') were based on the number of evaluable patients (per-protocol population) at the 'test-of-cure' (TOC) visit. Clinical cure was usually defined as the resolution or improvement of pretreatment signs and symptoms of infection at the TOC visit. Clinical failure was generally defined as the worsening of, or no improvement in, pretreatment signs and symptoms of the infection. The definition of bacteriological eradication was the complete eradication (absence) of baseline pathogens at the TOC visit.

Although >500 patients were enrolled in the clinical trials reviewed in this section, most trials were not powered to show statistically significant differences in efficacy between treatment groups. Statistical equivalence/nonequivalence of efficacy between treatments was usually assessed using pairwise confidence interval (CI) approaches. Only patients with baseline pathogens susceptible to study drugs were included in the majority of efficacy analyses.

4.1 Adults and Adolescents

Most trials of cefdinir (administered as a capsule formulation) in adults and adolescents have evaluated its clinical and bacteriological efficacy in the treatment of various types of lower or upper respiratory tract infections. Cefdinir has also been investigated in the treatment of patients with uncomplicated skin and skin structure infections in a single well designed trial.

Pregnancy, lactation, hepatic disease, baseline serum creatinine level >2 times normal or a CL_{CR} <30 mL/min (<1.8 L/h) or <50 mL/min (3 L/h),[79] antibacterial treatment within one week of starting trial medication, and baseline pathogen resistant to study drug were among the common exclusion criteria.[79-82] In individual trials, patients were evenly distributed across treatment groups by sex, race, presence/severity of presenting signs and symptoms. All antibacterial agents were administered orally.

4.1.1 Acute Bacterial Exacerbations of Chronic Bronchitis

Most of the pathogens that are commonly causative in patients with ABECB (e.g. *H. influenzae*, *M. catarrhalis* [including β-lactamase producers] and penicillin-susceptible *S. pneumoniae*), are susceptible to cefdinir *in vitro* (section 2.1).

A summary of randomised, double-blind, double-dummy, multicentre trials conducted in the US[79,81] and in Europe, the US, Australia and South Africa[82] comparing cefdinir with several other antibacterial agents is presented in table V. One of these trials also compared the efficacy of two dosage regimens of cefdinir.[82] Patients with ABECB (of presumed bacterial origin) with signs and symptoms of ABECB (e.g. sputum production and cough) and no evidence of pneumonia were enrolled in the trials.[79,81,82] Study populations consisted of both smokers and nonsmokers. Participants with a negative bacterial culture were withdrawn from the studies and excluded from the per-protocol populations at the TOC assessments. The pathogens most frequently cultured from sputum at baseline were β-lactamase-negative strains of *H. parainfluenzae* and *H. influenzae*, β-lactamase-positive strains of *M. catarrhalis*, *S. pneumoniae* and *S. aureus*.[79,81,82]

In all three trials, cefdinir demonstrated good clinical and bacteriological efficacy (table V). Clinical cure rates obtained with cefdinir 300mg twice daily for 5[79,81] or 10 days[82] or 600mg once daily for 10 days[82] ranged from 74–86.3% at the TOC assessment (table V).[81,82] Corresponding rates of bacterial eradication ranged from 81.3–90% (table V).

Cefdinir 300mg twice daily for 5[79] or 10 days,[82] or 600mg once daily for 10 days,[82] pro-

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Table V. Efficacy of oral cefdinir (CEF) in adults and adolescents with lower respiratory tract infections. Summary of randomised, double-blind, double-dummy, multicentre trials comparing CEF with other oral antibacterial agents

Study (year of publication)	No. of pts enrolled	Treatment regimen (mg) [duration in days]	Time from treatment initiation to TOC assessment (days)	Bacteriological response[a] (% of pathogens eradicated) [no. of pathogens isolated at baseline from evaluable pts]	Clinical cure[b] (% of pts) [no. of clinically and bacteriologically evaluable pts]
Acute bacterial exacerbations of chronic bronchitis					
Fogarty et al.[81]	278	CEF 300 bid [5]	7–11[c]	81.3 [193]	80.3[d] [142]
(2000)	270	CPZ 500 bid [10]	7–11[c]	83.8 [198]	71.9 [139]
Paster et al.[79]	291	CEF 300 bid [5]	12–19	88.1 [219]	86.3 [160]
(2000)	295	LOR 400 bid [7]	12–19	90.4 [251]	84.9 [166]
Van Herwaarden	349	CEF 600 od [10]	7–14[c]	90[e] [221]	81 [201]
et al.[82] (2000)	347	CEF 300 bid [10]	7–14[c]	85.3 [225]	74 [195]
	349	CFA 250 bid [10]	7–14[c]	87.7 [220]	80 [193]
Community-acquired pneumonia					
Drehobl et al.[80]	347	CEF 300 bid [10]	6–14[c]	92 [260]	89[f] [187]
(1997)	343	CFC 500 tid [10]	6–14[c]	93 [264]	86[f] [186]

a Defined as eradication of baseline pathogens at the TOC visit.

b Defined as resolution of pretreatment signs and symptoms of infection at the TOC visit.

c No. of days after the end of treatment.

d Statistically nonequivalent to the clinical cure rate in the CPZ group: 95% CI −1.6, 18.3 (limit for equivalence ±15%).

e Statistically nonequivalent to the bacteriological response rate in the twice-daily CEF group: 95% CI −1.4, 10.8 (limit for equivalence ±10%).

f Cure plus improvement ('clinical success').

bid = twice daily; **CFA** = cefuroxime axetil; **CFC** = cefaclor; **CPZ** = cefprozil; **LOR** = loracarbef; **od** = once daily; **pts** = patients; **tid** = three times daily; **TOC** = test-of-cure.

duced clinical cure rates at the TOC assessment that were statistically equivalent, using CI approaches, to those reported with loracarbef 400mg twice daily for 7 days[79] or cefuroxime axetil 250mg twice daily for 10 days.[82] In contrast, the clinical cure rate achieved with a 5-day course of cefdinir 300mg twice daily (80.3%) was not statistically equivalent to that reported for cefprozil 500mg twice daily for 10 days (71.9%), as the 95% CI around the difference in clinical cure rates for the two groups (−1.6, 18.3) was greater than predefined specific boundaries (±15%).[81]

Bacterial eradication rates in cefdinir-treated patients were similar to those reported for all comparators (table V).[79,81,82] However, in the trial reported by Van Herwaarden et al.,[82] the bacterial eradication rate in recipients of once-daily cefdinir was higher than that in the twice-daily cefdinir group (90.0% vs 85.3%; 95% CI −1.4, 10.8: specific boundaries for equivalence ±10%).

At long-term follow-up (28–42,[81] 26–40[79] and 21–35[82] days post-treatment), rates of clinical cure and bacteriological eradication in recipients of cefdinir were similar to those documented at the TOC evaluations. Clinical cure and bacteriological eradication rates were, respectively, 82% and 84%,[81] 89% and 96%,[79] and 93% (once-daily cefdinir), 95% (twice-daily cefdinir) and 95% (once-daily cefdinir), 99% (twice-daily cefdinir).[82]

4.1.2 Community-Acquired Pneumonia

Cefdinir provides good *in vitro* coverage of most of the bacterial pathogens that are commonly causative in CAP, including *S. pneumoniae* and the increasingly prevalent β-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*. Data on the efficacy of cefdinir in patients with CAP reviewed in this section are from a single randomised, double-blind, double-dummy trial (table V).[80]

In the trial reported by Drehobl et al.,[80] the efficacy of a twice-daily regimen of cefdinir was

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compared with that of cefaclor three times daily in adults and adolescents (aged ≥13 years) with radiologically confirmed and microbiologically documented (at least one respiratory tract pathogen at baseline) CAP. All patients presented with a cough and sputum production; other symptoms included shortness of breath and chest pain. Symptoms were generally of mild or moderate severity, although some patients did have severe symptoms. Patients were enrolled from 48 centres in the US from December 1991 to January 1995. The most common reason for exclusion from the efficacy analysis was the absence of a respiratory tract pathogen at admission. Of the pathogens isolated, 96% of *M. catarrhalis*, 22% of *H. influenzae* and 5% of *H. parainfluenzae* isolates were β-lactamase producers.[80]

Cefdinir was an effective treatment for patients with CAP and showed bacteriological and clinical efficacy similar to that of cefaclor (table V).[80] Clinical success, defined as cure ('absence or satisfactory remission of all admission signs and symptoms of CAP') plus improvement ('satisfactory remission but not complete disappearance of admission signs and symptoms') was achieved by 89% and 86% of evaluable patients in the cefdinir and cefaclor groups, respectively, at the TOC assessment 6–14 days post-treatment. Clinical success rates for the two treatment groups (table V) were equivalent based on 95% CIs (95% CI −7.6, 8.9%). Corresponding bacterial eradication rates were >90% and were also equivalent for the two groups (95% CI −5.9%, 3.3%). Rates of eradication of specific causative pathogens are shown in figure 3. At long-term follow-up 21–35 days post-therapy, bacteriological eradication rates were 99% (164 of 165 pathogens) and 100% (189 of 189) in the cefdinir and cefaclor groups, respectively.[80]

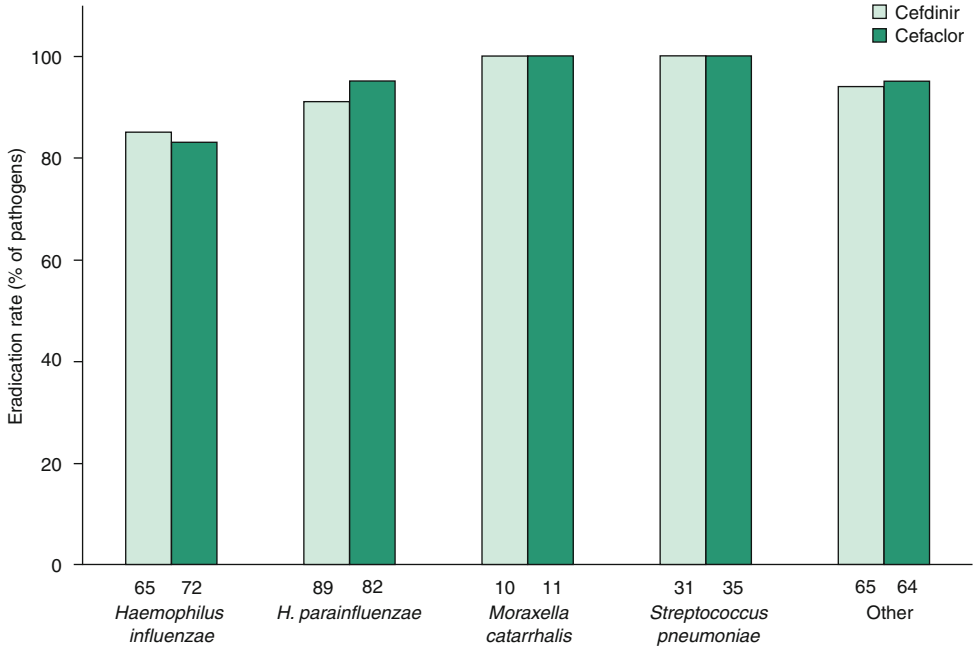

Fig. 3. Bacterial eradication rates by pathogen with oral cefdinir or cefaclor in adults or adolescents with community-acquired pneumonia (CAP).[80] Rates of eradication of *Haemophilus influenzae*, *H. parainfluenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae* and other pathogens (e.g. *Staphylococcus aureus*). Bacterial eradication rates reported at the test-of-cure visit (6–14 days after the end of treatment). Patients with CAP were randomised to receive treatment with cefdinir 300mg twice daily (n = 347) or cefaclor 500mg three times daily (n = 343) for 10 days in a double-blind, double-dummy, multicentre trial.[80] The numbers below the bars are the numbers of pathogens isolated at baseline.

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Table VI. Efficacy of oral cefdinir (CEF) in adults and adolescents with upper respiratory tract infections. Summary of randomised multicentre trials comparing CEF with oral amoxicillin/clavulanic acid (AMC) or penicillin V (PNV)

Study (blinding; year of publication)	No. of pts enrolled	Treatment regimen (mg) [duration in days]	Time of TOC assessment (no. of days post-therapy)	Bacteriological response[a] (% of pathogens eradicated) [no. of pathogens isolated at baseline from evaluable pts]	Clinical cure[b] (% of pts) [no. of evaluable pts]
Acute bacterial rhinosinusitis					
Gwaltney et al.[83] (sb; 1997)	585[c]	CEF 600 od [10]	7–14	89[d] [19[e]]; 78[d] [27[f]]; 100[d] [7[g]]; 100[d] [11[h]]	90[i] [474[j]]; 91 [167[k]]
	610[c]	CEF 300 bid [10]	7–14		87[i] [481[j]]; 89 [175[k]]
	603[c]	AMC[l] 500 tid [10]	7–14	100[d] [10[e]]; 57[d] [7[f]]; 100[d] [6[g]]; 67[d] [3[h]]	91[i] [491[j]]; 93 [195[k]]
Steurer and Schenk[84]	182[m]	CEF 600 od [10]	7–14	98 [123]	94.6 [93]
(sb; 2000)	198[m]	CEF 300 q12h [10]	7–14	90 [131]	89.6 [96]
	189[m]	AMC 500/125 q8h [10]	7–14	93 [138]	96.2 [106]
Streptococcal pharyngitis/tonsillitis					
Nemeth et al.[85]	305	CEF 600 od [10]	4–9	91.4*[n] [210]	94.8* [210]
(db; 1999)	304	CEF 300 bid [10]	4–9	91.7*[n] [217]	96.3* [217]
	310	PNV 250 qid [10]	4–9	83.4[n] [187]	88.9 [217]
Tack et al.[86]	278	CEF 300 bid [5] then PL [5]	5–10	88.5[n] [218]	89 [218]
(sb; 1998)	280	PNV 250 qid [10]	5–10	82.2[n] [214]	84.6 [214]

a Defined as eradication of baseline pathogens at the TOC visit.

b Defined as resolution of pretreatment signs and symptoms of infection at the TOC visit.

c Pooled number of pts with acute community-acquired bacterial rhinosinusitis enrolled in one US and one European trial. At enrolment, 698 pts in the US study and all 569 pts in the European study underwent antral puncture. Sinus aspiration was optional in the US study and mandatory in the European study.

d 10–30 days after the initiation of treatment (pooled data for CEF regimens).

e No. of strains of *Streptococcus pneumoniae* isolated from sinus aspirate pretreatment.

f No. of strains of *Haemophilus influenzae* isolated from sinus aspirate pretreatment.

g No. of strains of *Moraxella catarrhalis* isolated from sinus aspirate pretreatment.

h No. of other streptococci isolated from sinus aspirate pretreatment.

i Cure plus improvement.

j Clinically evaluable pts.

k Evaluable pts with positive cultures at admission.

l Dose of clavulanic acid not stated.

m All pts had acute maxillary rhinosinusitis.

n Eradication of *S. pyogenes.*

bid = twice daily; **db** = double-blind; **od** = once daily; **PL** = placebo; **pts** = patients; **qid** = four times daily; **q8h** = every 8 hours; **q12h** = every 12 hours; **sb** = single-blind; **tid** = three times daily; **TOC** = test-of-cure; * $p \leq 0.02$ vs PNV.

4.1.3 Acute Bacterial Rhinosinusitis

The majority of cases of acute bacterial rhinosinusitis are the result of bacterial invasion of the sinuses after a viral infection of the upper respiratory tract (reviewed by Gwaltney et al.[83]). The most common bacteria isolated from sinus aspirates are usually *H. influenzae*, *M. catarrhalis* (including β-lactamase-producing strains) and *S. pneumoniae*; *S. aureus* may also be causative. A summary of two randomised trials[83,84] comparing the efficacy of cefdinir with that of amoxicillin/clavulanic acid in adults and adolescents with acute bacterial rhinosinusitis is presented in table VI. Pretreatment and post-treatment sinus aspiration and culture was performed for all[84] or a subset of patients (table VI)[83] to determine bacterial eradication rates. The most

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common causative pathogens were *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*.[83,84]

Administered at dosages of 600mg once daily or 300mg twice daily for 10 days,[83,84] cefdinir showed similar efficacy to that of standard regimens of amoxicillin/clavulanic acid at the TOC visit 7–14 days post-treatment (table VI). Clinical response rates remained high (90.2%, 89.5% and 92.3% for cefdinir once daily, cefdinir twice daily and amoxicillin/clavulanic acid, respectively) 3–5 weeks post-treatment in the larger trial.[83] Bacteriological eradication results 10–30 days after the initiation of treatment for the patients from whom sinus aspirate culture results were available pretherapy are presented in table VI.[83]

4.1.4 Streptococcal Pharyngitis/Tonsillitis

Pharyngitis caused by *S. pyogenes* (group A β-haemolytic streptococci) requires appropriate antibacterial treatment to shorten its course and decrease the risk of suppurative complications, such as rheumatic fever (reviewed by Nemeth et al.[85]). Cefdinir shows excellent *in vitro* activity against *S. pyogenes* (see section 2.1.1) and penetrates well into tonsillar tissue (see section 3.2). In two randomised trials, one double-blind[85] and the other single- (investigator-) blind,[86] cefdinir courses of 5[86] or 10[85] days' duration showed good clinical efficacy (cure rates 89–96.3%) and produced high rates of *S. pyogenes* eradication (88.5–91.7%) at the TOC assessments (table VI). Both of the 10-day cefdinir regimens (300mg twice daily or 600mg once daily) investigated in the larger of the two trials[85] produced significantly higher clinical cure and *S. pyogenes* eradication rates than did penicillin V (phenoxymethylpenicillin) [$p \leq 0.02$ for all comparisons]. The 5-day course of cefdinir 300mg twice daily evaluated by Tack et al.[86] showed efficacy (at the TOC evaluation) equivalent to that of a standard 10-day course of penicillin V 250mg four times daily.

4.1.5 Uncomplicated Skin and Skin Structure Infections

Based on CI analysis, a 10-day course of cefdinir 300mg twice daily had clinical and bacteriological efficacy statistically equivalent to that of cefalexin 500mg four times daily for 10 days in adults and adolescents (aged ≥13 years) with skin and skin structure infections (e.g. abscesses, infected burns, cellulitis, infected dermatitis) in a randomised, double-blind trial conducted in multiple US centres (table VII).[87] Although >900 patients were recruited into the trial, < 50% of patients enrolled in each group were included in the efficacy assessments (table VII), primarily because they were found to have negative bacterial cultures at baseline. In addition, those patients requiring surgical intervention >24 hours after treatment initiation were regarded as 'treatment failures' and were also excluded from the efficacy-evaluable population. The most common pathogen at baseline was *S. aureus*, which was identified in about one-third of patients in each group. Overall, significantly more baseline pathogens were resistant to cefalexin than to cefdinir.[87]

At the TOC assessment 7–16 days post-therapy, successful clinical responses (clinical cure plus im-

Table VII. Efficacy of oral cefdinir (CEF) in adults and adolescents with uncomplicated skin and skin structure infections. Summary of a randomised, double-blind, multicentre trial comparing CEF with cefalexin (CFX)

Study (year of publication)	No. of pts enrolled	Treatment regimen (mg) [duration in days]	Time of TOC assessment (no. of days post-therapy)	Bacteriological response[a] (% of pathogens eradicated) [no. of pathogens isolated at baseline from evaluable pts]	Clinical success[b] (% of pts) [no. of clinically and bacteriologically evaluable pts]
Tack et al.[87] (1998)	474	CEF 300 bid [10]	7–16	93 [215]	88 [178]
	478	CFX 500 qid [10]	7–16	89 [247]	87 [204]

a Defined as eradication of baseline pathogens at the TOC visit.

b Cure plus improvement, defined as disappearance or satisfactory remission of pretreatment clinical signs and symptoms of infection at the TOC visit.

bid = twice daily; **pts** = patients; **qid** = four times daily; **TOC** = test-of-cure.

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Table VIII. Efficacy of oral cefdinir (CEF) in paediatric patients (pts) aged 6mo–12y with acute otitis media with effusion. Summary of randomised, single-blind (i.e. investigator-blind) multicentre trials comparing CEF (administered as a suspension) with other antibacterial agents

Study (year of publication)	No. of pts. enrolled (median age in y)	Treatment regimen (mg/kg/day) [duration in days]	No. of divided doses/day	Time of TOC assessment (no. of days post-therapy)	Clinical cure at TOC visit[a] (% of pts) [no. of evaluable pts]	Clinical cure or improvement at TOC visit (% of pts) [no. of clinically evaluable pts]
Comparisons with amoxicillin/clavulanic acid (AMC)						
Adler et al.[88]	203 (4.7)	CEF 14 [10]	2	11–16	73.9 [203]	88.7 [203]
(2000)	195 (4.5)	CEF 14 [10]	1	11–16	76.4 [195]	90.8 [195]
	197 (4.7)	AMC[b] 40 [10]	3	11–16	68.5 [197]	89.8 [197]
Block et al.[89][c]	128 (1.8)	CEF 14 [10]	2	11–27		66.4 [101]; 80.2[d] [101]
(2000)	128 (1.9)	CEF 14 [10]	1	11–27		71.5 [102]; 83.3[d] [102]
	128 (2.8)	AMC 40/10 [10]	3	11–27		69 [100]; 86[d] [100]
Comparison with cefprozil (CPZ)						
Block et al.[90]	219 (3)	CEF 14 [5]	2	11–16	65.3 [190]; 80[d] [190]	
(2000)	216 (3)	CPZ 30 [10]	2	11–16	64.5 [183]; 82.5[d] [183]	

a Defined as the resolution of pretreatment signs and symptoms of infection at the TOC visit.

b Dose of clavulanic acid not stated.

c Tympanocentesis study.

d At the 'end of therapy' assessment 2–4 days after the end of treatment[89] or on days 9–11.[90]

TOC = test of cure.

provement) were documented in 88% and 87% of cefdinir and cefalexin recipients, respectively; corresponding bacteriological eradication rates were 93% and 89% (table VII).[87]

4.2 Paediatric Patients

The efficacy of cefdinir in paediatric patients (aged 6 months to 12 years) with various types of community-acquired infections has been established in several randomised, multicentre, single- (investigator-) blind, active-control trials. In all trials, cefdinir and comparator agents were administered as suspension formulations. Documented hepatic disease, previous hypersensitivity to β-lactams, baseline pathogen resistant to study drugs, elevated hepatic enzymes (>2 times the upper limit of normal), and elevated serum creatinine (>1.5 times the upper limit of normal) or a CL_{CR} value of <30 mL/min (<1.8 L/h) were among the exclusion criteria in some trials.[88-93]

4.2.1 Acute Otitis Media

The most common causative bacterial pathogens in paediatric patients with acute otitis media are *S. pneumoniae*, which is the leading pathogen isolated in 25–50% of cases, *H. influenzae* (incidence 15–35%) and *M. catarrhalis* (3–20%).[94,95] Respiratory viruses with or without bacterial pathogens are causative in approximately 20% of middle ear fluids.[95] The presence of fluid in the middle ear together with at least one sign or symptom of systemic or local disease are defining features of acute otitis media.[95]

Cefdinir has been evaluated in three randomised clinical trials in acute otitis media, two comparing its efficacy with that of amoxicillin/clavulanic acid[88,89] and the third a comparison with cefprozil[90] (table VIII). Erythema of the tympanic membrane, middle ear effusion (corroborated by tympanometry) in one or both ears and other signs and symptoms of acute otitis media were common inclusion criteria.[88-90] Signs and symptoms of acute otitis media included irritability, anorexia, decreased hearing, irritability and vertigo. Patients with evidence of chronic otitis media, chronic middle ear effusion and/or perforation of either tympanic membrane were ineligible for enrolment in the trials. In addition, use of a topical aural medication within two days of the start of the trial was not permitted.[88-90] One of the trials was a tympa-

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nocentesis trial in which causative pathogens were identified at baseline.[89]

Patient age and severity of acute otitis media are usually inversely related and this may account for lower rates of clinical response in younger patients with more severe disease than their older counterparts. For this reason, patient age should be considered when assessing outcomes of patients in clinical trials.[96,97] Percentages of patients with clinical cure (resolution of signs and symptoms) and/or cure or improvement (partial disappearance or improvement of signs and symptoms) were reported at the TOC visit 11–16[88,90] or 11–27[89] days post-treatment (table VIII).

Cefdinir and amoxicillin/clavulanic acid, each given for 10 days, showed statistically equivalent clinical efficacy in the two trials shown in table VIII.[88,89] At the TOC visit, rates of clinical cure or improvement ranged from 66.4–90.8% with cefdinir (once or twice daily), compared with 69% and 89.8% with amoxicillin/clavulanic acid.[88,89] In the tympanocentesis study conducted by Block et al.,[89] the presumptive rate of eradication of *S. pneumoniae* at the end of treatment was significantly lower with cefdinir twice daily than with amoxicillin/clavulanic acid (55.2% vs 89.5%; $p = 0.0019$); the corresponding rate with cefdinir once daily was 80%. *M. catarrhalis* eradication rates were 85.7%, 58.3% and 50% for cefdinir twice daily, cefdinir once daily and amoxicillin/clavulanic acid, and rates of eradication of *H. influenzae* were 71.8%, 75% and 84%, respectively.

A 5-day course of cefdinir showed efficacy equivalent to that of 10 days' treatment with cefprozil in patients with nonrefractory acute otitis media.[90] Clinical cure rates at the TOC visit were, respectively, 65.3% and 64.5% for cefdinir and cefprozil. Higher clinical cure rates of 80% and 82.5% for cefdinir and cefprozil, respectively, were reported at the end of therapy visit on study days 9–11. Respective clinical cure rates at long-term follow-up (on study days 38–45) were 49.2% and 52.7%. When stratified by age group, clinical cure rates for both treatments arms were lowest in the youngest age group; for cefdinir, clinical cure rates by age group at the TOC visit were 49.3% (age <2 years), 73.1% (2–5 years) and 75.9% (6–12 years) and at the end of treatment were 71%, 85.1% and 83.3%.[90]

In a fourth recent investigator-blind nontympanocentesis trial, cefdinir 7 mg/kg twice daily for 5 days was as effective as amoxicillin/clavulanic acid 45 mg/kg/day (in 2 daily divided doses) for 10 days in the treatment of children (aged 6 months–6 years) with clinically diagnosed acute otitis media.[98] Clinical cure rates 2–4 days after the end of treatment (the 'end of treatment' evaluation) for the cefdinir and amoxicillin/clavulanic acid groups were 88% and 86%, respectively; at follow up (20–23 days after the last dose of cefdinir and 15-18 days after the last dose of amoxicillin/clavulanic acid) clinical cure rates were 78% and 84%. Clinical cure rates (for both the clinically evaluable and intention-to-treat populations) were significantly ($p < 0.05$) higher with cefdinir than with amoxicillin/clavulanic acid in the subgroups of patients who received *S. pneumoniae* vaccination with Prevnar® before the start of treatment. At the end of therapy visit, clinical cure rates for the cefdinir and amoxicillin/clavulanic acid groups were 92% and 82% (clinically evaluable patients) and 86% and 75% (intention-to-treat population).[98]

4.2.2 Streptococcal Pharyngitis/Tonsillitis

Pharyngitis/tonsillitis caused by *S. pyogenes* is one of the most common community-acquired bacterial infections in paediatric patients. As with older patients, prompt treatment is required to expedite the resolution of symptoms and to prevent suppurative sequelae and acute rheumatic fever. Two randomised, investigator-blind trials, one conducted in centres in the US and Canada,[91] and the other in US centres only,[92] have compared the efficacy of cefdinir (for 5 or 10 days) with that of penicillin V (for 10 days), the standard recommended treatment (table IX). Inclusion criteria included sore/painful throat, pharyngeal erythema, positive rapid streptococcal antigen test. To be evaluable, patients had to have a positive culture of *S. pyogenes* at enrolment. Clinical cure was defined as the absence or satisfactory remission of all symptoms and signs of infection at the TOC visit; bacteriological success was

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Table IX. Efficacy of oral cefdinir (CEF) in paediatric patients (pts) aged 1–12y with streptococcal pharyngitis/tonsillitis. Summary of two randomised, single-blind (i.e. investigator-blind), multicentre trials comparing CEF (administered as a suspension) with penicillin V (PNV)

Study (year of publication)	No. of pts enrolled (median age in y)	Treatment regimen (mg/kg/day) [duration in days]	No. of divided doses/day	Time of TOC assessment (no. of days post-therapy)	Bacteriological response (% of patients with eradication of *Streptococcus pyogenes*) [no. of pathogens isolated at baseline from evaluable pts]	Clinical cure[a] (% of pts) [no. of evaluable pts]
Nemeth et al.[91]	264 (7.6)	CEF 14 [10]	1	4–9	94.3**[b] [228]	97.4*[c] [228]
(1999)	264 (7.0)	CEF 14 [10]	2	4–9	94.3**[d] [227]	96*[e] [227]
	264 (7.2)	PNV 40 [10]	4	4–9	70.0 [227]	86.3 [227]
Tack et al.[92]	240 (7.4)	CEF 14 [5]	2	5–10	89.7**[f] [224]	91.5 [224]
(1997)	242 (7.7)	PNV 40 [10]	4	5–10	71.8 [216]	90.7 [216]

a Defined as the absence or satisfactory remission of all symptoms and signs of infection at the TOC visit.
b 95% CI 17.6%, 30.9% vs PNV.
c 95% CI 6.1%, 15.9% vs PNV.
d 95% CI 17.5%, 30.9% vs PNV.
e 95% CI 4.6%, 14.8% vs PNV.
f 95% CI 10.7%, 25.1% vs PNV.
TOC = test-of-cure; * $p = 0.001$, ** $p < 0.001$ vs PNV.

the complete eradication of *S. pyogenes* at the same timepoint. CIs were used to assess the equivalence/nonequivalence of clinical and microbiological outcomes; p-values were also calculated to detect between-treatment differences.[91]

Rates of eradication of *S. pyogenes* (≥90%) with cefdinir 7 mg/kg twice daily for 5 or 10 days, or 14 mg/kg once daily for 10 days were significantly ($p < 0.001$) higher than eradication rates (≈70%) achieved with penicillin V at the TOC assessments (table IX). In addition, the clinical cure rates (≥96%) obtained with both 10-day regimens of cefdinir in the trial reported by Nemeth et al.[91] were significantly ($p = 0.001$) higher than that reported for the penicillin V group (86.3%). Both trials were also studied in consolidated analysis (performed by Pichichero and Gooch[99]) in which the superiority of 5- and 10-day courses of cefdinir over penicillin V was also shown at the TOC visits. At long-term follow up on study days 25–31, eradication of *S. pyogenes* in patients with successful bacteriological outcomes at the TOC visits was sustained in 98.2% of 554 patients who received cefdinir and 92.8% of 264 penicillin V recipients.[99]

4.2.3 Uncomplicated Skin and Skin Structure Infections

The efficacy of cefdinir in the treatment of uncomplicated skin and skin structure infections in paediatric patients has been evaluated in a single, randomised, investigator-blind comparative trial (table X).[93] At baseline, the most frequent pathogens identified were *S. aureus* and *S. pyogenes*. Impetigo (two-thirds of the population), infected dermatitis and wound infection were the most common infections. At the TOC visit, rates of clinical cure were similar with cefdinir (administered twice daily) and cefalexin (four times daily): 98.3% and 93.8%, respectively. Bacteriological eradication rates were also high and similar (>97%) for the two groups. Intention-to-treat analysis confirmed that the two drugs had similar clinical efficacy: clinical cure rates for cefdinir and cefalexin were 91.3% and 91.4%, respectively; bacteriological eradication rates were 95.6% and 91% ($p < 0.05$).[93]

5. Tolerability

The tolerability profile of cefdinir has been evaluated in numerous randomised clinical trials enrolling adults, adolescents (section 4.1) and paediatric patients (aged 6 months to 12 years) [section 4.2]. In addition, pooled tolerability data from clinical trials

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of cefdinir administered as a capsule (in adults and adolescents) or a suspension (paediatric patients) are reviewed in the manufacturer's prescribing information.[2]

Cefdinir was generally well tolerated by patients of all age groups, with most adverse events being mild and self-limiting. No reports of permanent disabilities or deaths have been attributed to treatment with cefdinir.[2] As with most antibacterials, pseudomembranous colitis, ranging in severity from mild to life-threatening, has occasionally been reported with cefdinir.[2] Overgrowth of *Clostridium difficile* should therefore be considered in patients presenting with diarrhoea during treatment.

5.1 Adults and Adolescents

5.1.1 General Profile

Pooled data from US trials show that diarrhoea (incidence 15%), nausea (3%) and headache (2%) were the most common adverse events recorded for the combined male and female population of adults and adolescents (n = 3841; 2108 females, 1733 males) receiving cefdinir capsules at therapeutic dosages (actual dosages not reported). [2]

Rash (0.9%), dyspepsia, flatulence and vomiting (0.7% incidence for each) were among the events reported by <1% but >0.1% of patients receiving the drug.[2] Consistent with the results of the pooled analysis, diarrhoea, which was usually mild, was the most common event in recipients of cefdinir in the clinical trials reviewed in section 4.1. Diarrhoea was reported by 7.8–33% of patients treated with cefdinir 300mg twice daily or 600mg once daily.[80-87] Overall, cefdinir treatment was discontinued due to adverse events in 1–6.1% of patients[79-87] Changes in laboratory values have also been observed in cefdinir-treated patients (n = 3841), occurring at an incidence of ≤2%. Increased levels of leucocytes in urine and increased urine protein were each reported in 2% of patients; increased γ-glutamyltransferase levels (study population n < 3841) and increased microhaematuria were each reported in 1% of patients, and 1% of patients had decreased lymphocyte levels.[2]

5.1.2 Comparative Tolerability

In randomised clinical trials (section 4.1), most adverse events (e.g. nausea and headache) in patients treated with cefdinir occurred at a similar incidence to those reported for recipients of cefaclor,[80] cefprozil,[81] cefuroxime axetil,[82] loracarbef,[79] penicillin V[86] and amoxicillin/clavulanic acid.[83,84] However, diarrhoea was reported by statistically significantly more recipients of cefdinir than of cefaclor (13.7% vs 5.3%; $p < 0.01$),[80] cefprozil (17% vs 6%; $p < 0.01$),[81] cefalexin (16% vs 7%; $p < 0.001$),[87] loracarbef (percentages not reported; $p = 0.001$),[79] and penicillin V (11.2% vs 6.4%; $p = 0.04$[86] and 17.1% vs 3.5%; $p \leq 0.01$[85]). In addition, the overall incidence of adverse events in cefdinir treatment groups was significantly higher than in recipients of cefaclor (35.2% vs 25.6%; $p < 0.005$),[80] loracarbef (30% vs 21%; $p = 0.008$),[79] cefalexin (26% vs 16%; $p < 0.001$)[87] and penicillin V (≈30% vs 15.5%; $p < 0.001$).[85] Nevertheless, rates of discontinuation due to adverse events were similar for cefdinir and the comparator groups in the majority of trials,[79-82,85-87] and, in two trials, discontinuation rates were lower with cefdinir than with

Table X. Efficacy of oral cefdinir (CEF) in paediatric patients (pts) aged 6mo to 12y with uncomplicated skin or skin structure infections. Summary of a randomised, single-blind, multicentre trial comparing CEF (administered as suspension) with cefalexin (CFX) suspension

Study (year of publication)	No. of pts enrolled	Treatment regimen (mg/kg/day) [duration in days]	No. of divided doses	Time of TOC assessment (no. of days post-therapy)	Bacteriological eradication[a] (% of pathogens eradicated) [no. of pathogens isolated at baseline from evaluable pts]	Clinical cure[b] (% of pts) [no. of clinically and bacteriologically evaluable pts]
Tack et al.[93]	196	CEF 14 [10]	2	7–14	99.4 [165]	98.3 [118]
(1997)	198	CFX 40 [10]	4	7–14	97.4 [156]	93.8 [113]

a Defined as eradication of baseline pathogens at the TOC visit.

b Defined as absence or satisfactory remission of all admission signs and symptoms at the TOC visit.

TOC = test-of-cure.

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amoxicillin/clavulanic acid.[83,84] In these two trials (in patients with acute bacterial rhinosinusitis), discontinuation rates due to adverse events were significantly lower in the combined groups of patients treated with cefdinir 600mg once daily (1%) or 300mg twice daily (3%) [$p < 0.002$],[83] and in recipients of cefdinir 600mg once daily (1.7%; $p = 0.02$)[84] than in recipients of amoxicillin/clavulanic acid (5%[83] and 6.3%[84]).

5.2 Paediatric Patients

5.2.1 General Profile

As in adults, diarrhoea was the most common adverse event (incidence 8%) in infants and children aged 6 months to 12 years treated with cefdinir suspension at therapeutic dosages (n = 1783; 806 females, 977 males).[2] In the pooled analysis, the incidence of diarrhoea in paediatric patients was lower than in adult recipients of cefdinir capsules (section 5.1).

Similarly, in clinical trials reviewed in section 4.2,[88-93,99] diarrhoea (incidence 2.9–15.9%) was the most common adverse event in infants and children receiving cefdinir suspension 14 mg/kg/day. Rash (incidence 3%) and vomiting (1%) were the only other events reported in ≥1% of patients.[2] Of the events documented in >0.1% and <1% of patients, cutaneous moniliasis (0.9%) and abdominal pain (0.8%) were the most common.[2] Changes in laboratory values of possible clinical significance occurred infrequently. These included increased lymphocyte levels (incidence 2%) and decreased bicarbonate levels (1%).

5.2.2 Comparative Tolerability

In the clinical trials reviewed in section 4.2, overall rates of adverse events in patients receiving cefdinir suspension 14 mg/kg/day were similar to those reported for recipients of cefprozil,[90] penicillin V[91,92,99] or cefalexin suspensions.[93] In addition, the incidence of diarrhoea in cefdinir-treated patients was broadly similar to that reported for recipients of cefprozil,[90] penicillin V suspension[91-93,99] or amoxicillin/clavulanic acid suspensions.[89] Cefdinir tended to be better tolerated overall than amoxicillin/clavulanic acid in patients participating in the larger of the two trials conducted in children with acute otitis media.[88,89] In this trial,[88] the overall rate of adverse events was significantly higher in the amoxicillin/clavulanic acid treatment group than in the recipients of cefdinir 14 mg/kg once daily (26.2% vs 16.7%; $p = 0.01$). Moreover, in the other trial in patients with acute otitis media,[89] diarrhoea was a significantly ($p < 0.001$) more frequent treatment-associated adverse event in patients treated with amoxicillin/clavulanic acid (35%) than in recipients of cefdinir 7 mg/kg twice daily (13%) or 14 mg/kg once daily (10%).

In the trials reviewed in section 4.2, rates of treatment discontinuation reported for cefdinir recipients were similar to those reported for patients treated with cefprozil[90] or penicillin V.[91,92,99] In one of the two trials in patients with acute otitis media,[88] the rate of treatment discontinuation was significantly ($p = 0.02$) lower in the recipients of cefdinir 14 mg/kg once daily (4%) than in the amoxicillin/clavulanic acid group (10%). Treatment discontinuation rates were similar for cefdinir 7 mg/kg twice daily, cefdinir 14 mg/kg once daily and amoxicillin/clavulanic acid in the other trial.[89] Adherence to courses of treatment with antibacterial suspensions depends on a number of factors, including palatability.[100-104] The palatability of cefdinir compared favourably with that of amoxicillin/clavulanic acid, cefprozil and azithromycin suspensions in randomised comparative trials (see section 7).[102]

6. Dosage and Administration

Cefdinir is approved in the US for the treatment of adults, adolescents and paediatric patients (aged ≥6 months) with specific mild-to-moderate infections caused by susceptible strains of designated pathogens.[2] The drug is formulated as 300mg capsules and as a powder for reconstitution with water to produce a strawberry-flavoured suspension containing 125mg in 5mL. Once reconstituted, the suspension has a shelf life of 10 days and can be stored at controlled room temperature. Both formulations may be administered without regard to meals (see section 3.1). Recommended dosages of cefdinir for

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the treatment of adults, adolescents and paediatric patients are provided in table XI.

An interval of ≥2 hours between administration of cefdinir and both aluminium/magnesium-containing antacids and iron supplements is recommended because the rate and extent of absorption of cefdinir are substantially reduced when it is coadministered with these agents (see section 3.5).

Dosage modification is required for patients with transient or persistent renal impairment (CL_{CR} <30 mL/min; 1.8 L/h) [see section 3.4]. In adults and adolescents, the dosage should be reduced to 300mg once daily. In paediatric patients (CL_{CR} <30 mL/min/1.73m^2) the recommended dosage is 7 mg/kg (to a maximum of 300mg) once daily.

Table XI. Recommended dosages of oral cefdinir for the treatment of adults, adolescents or paediatric patients with various types of infections[2]

Infection type	Dosage	Duration of treatment (days)
Adults and adolescents (aged ≥13y)		
Community-acquired pneumonia	300mg q12h	10
Acute bacterial exacerbations of chronic bronchitis	300mg q12h	5–10
	600mg q24h	10
Acute maxillary rhinosinusitis	300mg q12h or 600mg q24h	10
Pharyngitis/tonsillitis	300mg q12h	5–10
	600mg q24h	10
Uncomplicated skin and skin structure infections	300mg q12h	10
Paediatric patients (aged 6mo–12y)		
Acute bacterial otitis media	7 mg/kg q12h	5–10
	14 mg/kg q24h	10
Acute maxillary rhinosinusitis[a]	7 mg/kg q12h	10
	14 mg/kg q24h	10
Pharyngitis/tonsillitis	7 mg/kg q12h	5–10
	14 mg/kg q24h	10
Uncomplicated skin and skin structure infections	7 mg/kg q12h	10

a The efficacy of cefdinir has not been established in clinical trials in paediatric patients with acute maxillary rhinosinusitis. However, it is approved for use in this population because the pathophysiology of acute maxillary rhinosinusitis is similar in adults, adolescents and paediatric patients.[105]

q12h = every 12 hours; **q24h** = every 24 hours.

Some cephalosporins have been associated with triggering seizures, particularly in patients with renal impairment not receiving a reduced dosage of the drug. As with other cephalosporins, cefdinir should be discontinued if a patient has a seizure thought to be associated with the drug.[2]

7. Place of Cefdinir in the Management of Mild-to-Moderate Bacterial Infections

The original source of a cephalosporin, discovered more than 50 years ago, was a strain of *Cephalosporium acremonium*. Since then, modification of the cephem nucleus has led to the development of numerous oral and parenteral cephalosporins.[106-108] Oral cephalosporins have been in clinical use for more than 30 years and have established efficacy in a wide variety of bacterial infections in both community and hospital settings. The large number of cephalosporin derivatives developed over time has necessitated differentiation of agents in various ways, including the 'cephalosporin generation' system,[106-108] which classifies agents largely on the basis of chemical structure, spectrum of *in vitro* antibacterial activity and pharmacokinetic profile.

Although the first-generation oral cephalosporins (e.g. cefalexin and cefradine) have well-documented efficacy, they require frequent administration (e.g. three or four times daily) and there are important limitations in their antibacterial spectra. For example, these agents are usually inactive against β-lactamase-producing strains of *H. influenzae* and *M. catarrhalis* and provide only limited coverage against β-lactamase-negative strains of these species (reviewed by Bergogne-Berezin[106]). By comparison, the second-generation oral cephalosporins (e.g. cefaclor and cefuroxime axetil) have broader antibacterial spectra, including some β-lactamase-producing strains of bacteria, but are less active than first-generation agents against Gram-positive cocci.[106]

Cefdinir is a third-generation cephalosporin with documented efficacy in a wide variety of mild-to-moderate bacterial infections (see section 4). The drug has a well-defined spectrum of antibacterial

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activity that includes many common community-acquired pathogens (see section 2). Compared with first- and second-generation cephalosporins, cefdinir has an expanded spectrum of antibacterial activity encompassing many pathogens associated with respiratory tract and skin infections. Importantly, the drug shows good activity against increasingly prevalent β-lactamase-producing strains of bacteria, including *H. influenzae* and *M. catarrhalis* (see section 2.1.2) as well as other common pathogens, such as *S. pyogenes* and *S. aureus* (see section 2.1.1).

S. pneumoniae is possibly the most significant community-acquired pathogen because of its high incidence and association with considerable morbidity and mortality.[109] The emergence of penicillin resistance among *S. pneumoniae* over recent years is of serious concern and the incidence of penicillin-resistant pneumococci continues to increase worldwide.[24,110,111] In a recent surveillance study conducted during the winter of 1999/2000,[24] 21.5% of clinical isolates of *S. pneumoniae* (n = 1531) in the US were resistant to penicillin (MIC ≥2 mg/L). In the SENTRY surveillance program (1997–9),[112] rates of resistance among pneumococci were 14% in the US, 6.8% in Canada and 11.7% in Latin America. In Latin American countries, there is wide variation in rates of penicillin resistance among pneumococci, with the highest rates found in Mexico (23.3%) and Chile (27.3%) and the lowest rates (<2%) detected in Brazil (1997/1998 figures).[113] Cefdinir shows good activity against penicillin-susceptible strains of *S. pneumoniae* (see section 2.1.1) and is approved for use in the treatment of certain infections caused by such strains.[2] However, it has variable activity against penicillin-intermediate strains and poor activity against penicillin-resistant strains, and is not approved for the treatment of infections caused by these pathogens.

While the *in vitro* activity of cefdinir is broadly similar to that of cefuroxime and cefpodoxime, some points of difference have been noted by several investigators.[37,108,114] For example, cefdinir has shown better activity than cefpodoxime against methicillin-susceptible staphylococci in some investigations (reviewed by Felmingham[108]) and appears to be more stable to hydrolysis by some plasmid-encoded β-lactamases than cefuroxime.[37]

When selecting an appropriate cephalosporin or other type of antibacterial for the treatment of a patient with a mild-to-moderate bacterial infection, the clinician has a wide range of drugs to choose from and this can make treatment selection quite difficult. As well as antibacterial spectrum, local resistance patterns and local prescribing policies, other important factors influence the choice of agent for the management of a particular infection (table XII).

Cefdinir attains C_{max} 2–3 hours after oral administration (see section 3) and its elimination kinetics allow for convenient once- or twice-daily administration, depending on the type of infection being treated. In addition, it is widely distributed in various respiratory tract tissues and fluids as well as skin blister and middle ear fluids (see section 3.2). Although data on the relationship between the pharmacodynamics and pharmacokinetics of cefdinir are limited at present, available information suggests that it achieves clinically relevant concentrations (against common respiratory tract pathogens) in respiratory tract tissues and fluids for a least 4 hours (see section 3.2).[74] As well as tablets, cefdinir is available as an oral suspension, which has

Table XII. Factors influencing the choice of an appropriate oral antibacterial agent for the treatment of patients with mild-to-moderate bacterial infections

Spectrum of antibacterial activity (e.g. good activity against the major pathogens commonly causative in community-acquired infections of the respiratory tract or skin)
Local patterns of bacterial resistance (e.g prevalence of β-lactamase-positive strains of *Haemophilus influenzae*)
Time that drug concentrations are above minimum inhibitory concentrations for a specific pathogen in the target tissue/fluid
Pharmacokinetic profile (e.g. good penetration into target tissues and fluids; plasma half-life allowing for convenient dosage regimen [once- or twice-daily administration], thereby optimising compliance)
Evidence of good clinical and bacteriological efficacy in patients with infections
Palatability of suspension formulations
Potential for good compliance
Duration of treatment
Tolerability profile
Cost

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a better taste and a more convenient dosage regimen than some other oral antibacterial suspensions.[102] Thus, oral cefdinir suspension offers the potential for good compliance in paediatric patients.

The clinical and bacteriological efficacy of cefdinir has been established in numerous well-designed comparative trials in adults, adolescents and paediatric patients (see section 4). The drug has a well-characterised tolerability profile and is usually well tolerated (see section 5). Diarrhoea, which was generally mild and seldom prompted treatment discontinuation, was the most common adverse event in comparative trials (see sections 5.1.2 and 5.2.2) and in pooled data from US trials (incidence 15% and 8% in adults/adolescents and paediatric patients, respectively) [see sections 5.1.1 and 5.2.1]. Although the incidence of diarrhoea was higher with cefdinir than with some comparators, rates of treatment discontinuation due to adverse events tended to be similar for cefdinir and comparators. Moreover, in several trials, rates of treatment discontinuation were lower with cefdinir than with amoxicillin/clavulanic acid.[83,84,88]

In adults and adolescents with pathogens susceptible to study drug at baseline, cefdinir generally showed clinical and/or bacteriological efficacy equivalent to that of cefprozil, loracarbef and cefuroxime axetil in ABECB, cefaclor in CAP, amoxicillin/clavulanic acid in acute bacterial rhinosinusitis, and cefalexin in uncomplicated skin and skin structure infections in randomised controlled trials (see section 4.1). In one of the trials in patients with ABECB, a 5-day course of treatment with cefdinir produced a higher clinical cure rate than a 10-day course of cefprozil: clinical cure rates for the two groups were not equivalent based on 95% CIs (see section 4.1.1).[81] Cefdinir was also a beneficial treatment for adults and adolescents with streptococcal pharyngitis/tonsillitis and showed efficacy at least as good as that of penicillin V (see section 4.1.4). The results of several of these studies confirm that 5-day courses of cefdinir can be used to treat patients with ABECB or streptococcal pharyngitis. Indeed, the duration of treatment with cefdinir (5 days) was shorter than that with cefprozil (10 days),[81] loracarbef (7 days)[79] and penicillin V (10 days).[86] Furthermore, cefdinir 300mg twice daily for 10 days was as effective as cefdinir 600mg once daily for 10 days in the treatment of patients with acute bacterial rhinosinusitis or streptococcal pharyngitis (see sections 4.1.3 and 4.1.4). Recent updated guidelines for the treatment of bacterial rhinosinusitis recommend cefdinir as a first-line treatment option for adults and children with mild disease who have received no antibacterial treatment during the previous 4–6 weeks.[115]

As in adults and adolescents, cefdinir produced good bacteriological and clinical responses in paediatric patients with bacterial infections of the upper respiratory tract or skin (see section 4.2). Favourable bacteriological and/or clinical responses at TOC visits were obtained with cefdinir for 5 or 10 days in paediatric patients with acute otitis media with effusion; once- or twice-daily regimens of cefdinir showed efficacy equivalent to 10-day courses of amoxicillin/clavulanic, administered three times daily, or twice-daily cefprozil. Notably, one of the studies was a tympanocentesis study that evaluated pathogen-directed rather than empirical treatment.[89] Cefdinir has not been compared with newer formulations/dosages of amoxicillin/clavulanic acid[96] in patients with acute otitis media because the indicated patient populations are inherently different. Management of paediatric patients with acute otitis media with effusion is, however, controversial.[116-119] Many clinicians advocate withholding antibacterial treatment, as the condition can resolve spontaneously within 7–10 days in 70–80% of cases.[96,120] While this may often be appropriate, deferred treatment can result in serious sequelae, including mastoiditis, hearing loss and meningitis if patients requiring antibacterial therapy cannot be identified quickly.[96,117] *S. pneumoniae* is the most common causative pathogen.[116,121,122] In the US, it has been estimated that more than 16.8 million episodes of acute otitis media occur each year in infants and children aged ≤6 years and *S. pneumoniae* (often penicillin-resistant) is causative in 35–45% of cases.[94] Antibacterial therapy therefore has an important role in the management of these

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patients.[121,123] Clinical evidence supports the use of cefdinir as a second-line therapy for acute otitis media, especially for patients who are hypersensitive to penicillin and for those presenting with recurrent acute otitis media within four weeks of treatment.[90] A recent evidence-based clinical practice guideline for the management of infants and children aged 2 months to 12 years with uncomplicated acute otitis media[124] advocates cefdinir as a treatment option for patients with a non-type I allergy to penicillin; cefdinir treatment may be initiated either at diagnosis or after clinically defined treatment failure (48–72 hours after an initial observation management approach).

Penicillin V administered for 10 days is the standard first-line therapy for paediatric patients with streptococcal tonsillitis/pharyngitis because of its narrow spectrum of antibacterial activity, well-established efficacy, low cost and generally favourable tolerability profile.[125,126] However, reports of decreased penicillin efficacy over recent years, partly due to the emergence of β-lactamase-producing bacteria and poor patient compliance,[126] have led to the evaluation of other antibacterials suitable for the treatment of this infection. Although cefdinir is not recommended as a first-line treatment for streptococcal tonsillitis/pharyngitis in US treatment guidelines, it has shown good efficacy and, when administered once- or twice-daily for 10 days or twice daily for 5 days, produced higher rates of eradication of *S. pyogenes* than 10 days' treatment with penicillin V four times daily in two comparative trials (see section 4.2.2).[91,92] Cefdinir appears to be a second-line option for paediatric patients with streptococcal tonsillitis/pharyngitis and may be of particular benefit for the treatment of those allergic to penicillin V. Furthermore, as noted by several investigators,[127-129] there is a good rationale for prescribing the shorter (5-day) cefdinir regimen in terms of improving compliance, thereby reducing the risk of clinical and bacteriological failure and the emergence of resistant bacterial strains that can occur in patients receiving longer courses of treatment. The cost of treatment is an important consideration for the clinician and the acquisition cost of cefdinir is substantially higher than that of penicillin. Nevertheless, its cost may be partly offset by cost benefits achieved by 5-day courses of treatment, arising as a result of improved patient satisfaction and probable higher rates of adherence to treatment.[130]

A number of factors influence compliance with antibacterial therapy regimens and ultimately treatment success, and adherence issues may be key determinants in the choice of an antibacterial agent.[103] Adherence to courses of antibacterial suspension formulations depends on a number of factors, including tolerability, frequency of administration and palatability.[100-104] Selection of an agent with an infrequent administration schedule together with a short course should encourage adherence to treatment in paediatric patients. Moreover, for infants and children, a pleasant tasting medicine may be as important as a convenient dosage regimen and can be one of the most critical factors influencing adherence.[103] The taste of cefdinir suspension has been described as strawberry milkshake flavoured and, in a series of six randomised single-blind, crossover trials, was rated as tasting 'good or really good' by 85% of 715 paediatric recipients aged 4–8 years.[102] Overall, these children preferred the taste of cefdinir to that of amoxicillin/clavulanic acid, cefprozil or azithromycin, each of which were rated as tasting 'good or really good' by 63% of the recipients.[102] The order of taste preference was: cefdinir > azithromycin > cefprozil > amoxicillin/clavulanic acid.

In conclusion, cefdinir is a third-generation cephalosporin with a broad spectrum of antibacterial activity encompassing pathogens that are commonly causative in infections of the respiratory tract or skin and skin structure. Depending on the infection being treated, cefdinir can be administered as a convenient once- or twice-daily 5- or 10-day regimen. Clinical evidence indicates that cefdinir is an effective and generally well tolerated drug with superior taste over comparator antibacterial agents and is therefore a good option for the treatment of adults, adolescents and paediatric patients with specific mild-to-moderate respiratory tract or skin infections, particularly in areas where β-lactamase-mediated resis-

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tance among common community-acquired pathogens is a concern.

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