Introduction

Dirithromycin is a semi-synthetic macrolide antibiotic for oral use. Dirithromycin is converted non-enzymatically during intestinal absorption into the microbiologically active moiety erythromycylamine. This active form, erythromycylamine, is rapidly distributed in the tissues and the drug persists in lung tissue for 94 h after a single dose. The plasma elimination half-life of 44 h permits once-daily dosing.

Dirithromycin is active in vitro against bacteria that cause bronchitis, including Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Mycoplasma pneumoniae and Chlamydia pneumoniae. Dirithromycin for 7–14 days is effective for community-acquired pneumonia, streptococcal pharyngitis, acute bronchitis and acute exacerbations of chronic bronchitis due to sensitive strains of micro-organisms, and skin-structure infections due to Staphylococcus aureus. Because dirithromycin persists in pulmonary tissues, shorter treatments may be effective for mild to moderate respiratory diseases.

In these two randomized, well-controlled, double-blind clinical trials, we hypothesized that 5 days of dirithromycin would be as effective as 7 days of erythromycin for acute exacerbations of chronic bronchitis.

Materials and methods

Ethics committee approval was received at every study site and patients were enrolled when informed consent was obtained. All patients who gave consent and were randomised to receive dirithromycin (500 mg od) for 5 days and 526 patients were randomized to receive erythromycin (250 mg qid) for 7 days. Clinical and bacteriological responses were assessed 3–5 days after therapy and at termination from the study. Adverse events were collected from both groups and compared with each other, before and after treatment. Of the 690 patients clinically appraisable at the post-therapy visit, 298 (84.2%) dirithromycin-treated patients and 270 (80.4%) erythromycin-treated patients showed a favourable response. At termination, 273 (77.1%) dirithromycin-treated patients and 243 (72.3%) erythromycin-treated patients showed a favourable response. The microbiological cure was equivalent in the two groups (75% of dirithromycin-treated patients and 74.1% of erythromycin-treated patients showed a favourable response at termination). After therapy, dirithromycin was as effective as erythromycin in eradicating Streptococcus pneumoniae (77.8% vs 90.9%), Haemophilus influenzae (71.7% vs 72.2%), Moraxella catarrhalis (93.3% vs 88.9%) and Staphylococcus aureus (81.8% vs 82.1%). Although not statistically significant, fewer dirithromycin-treated patients reported adverse events than did erythromycin-treated patients. Nausea (6.8% vs 7.8%), headache (7.3% vs 8.2%) and diarrhoea (6.6% vs 9.5%) were the most frequently reported adverse events in both groups. In the treatment of acute exacerbations of chronic bronchitis, 5 days of dirithromycin is as effective as 7 days of erythromycin.
ized to a treatment group were included in the intent-to-treat safety analysis, even if they were not treated with the study drug.

Inclusion criteria

Patients were included if they were ≥12 years of age with an acute exacerbation of chronic bronchitis, and weighed ≥37 kg and were able to swallow tablets. Women of child-bearing age required a negative pregnancy test before enrolment and use of a reliable method of birth control during treatment and for 30 days afterwards. Concomitant medication needed for the treatment of underlying diseases or conditions was acceptable, except for systemic antibiotics.

Exclusion criteria

Exclusion criteria included any condition that in the opinion of the investigator could preclude evaluation of response; known or anticipated requirement of systemic antibiotics (other than the study drug) during the study period; hypersensitivity to macrolides; use of any systemic antimicrobial within 7 days before enrolment; participation in any previous dirithromycin study; participation in any other study involving investigational agents within 30 days before enrolment in this study. Nursing and pregnant women were also excluded. Patients with pneumonia, determined by an infiltrate on chest X-ray, were excluded.

Chronic bronchitis defined

Chronic bronchitis was defined as a productive cough present most days during ≥3 consecutive months for ≥2 consecutive years. An exacerbation was defined as a significant increase in sputum production and in the frequency and severity of cough. Additionally, two or more of the following diagnostic findings were required for study entry: fever (≥38°C), cough, dyspnoea, rhonchi, or coarse râles. Microscopic evidence of infection, pre-therapy sputum with ≥25 WBC and ≤10 epithelial cells (magnification ×100), was required.

Patient terminations

If a patient required a systemic antibiotic after the protocol was initiated, the study drug was discontinued and sputum cultures and laboratory tests were obtained before administration of a new antibiotic. A patient requiring a new antibiotic for bronchitis during the period of study drug administration was classified as a symptomatic failure or relapse. If another systemic antibiotic was taken for any reason other than the study indication, the patient qualified only for the intent-to-treat efficacy and safety evaluation. Patients were also terminated from the study if they had an adverse event prohibiting completion of the protocol, if they requested termination, or if their physician requested termination. When possible, patients who withdrew from the study had laboratory tests and sputum Gram's stain and culture performed at the time of termination.

Study drug administration

Patients randomized to dirithromycin received two 250 mg dirithromycin tablets once daily for 5 consecutive days and one dummy tablet, identical in size and shape to erythromycin, every 6 h for 7 days. Patients randomized to erythromycin received one 250 mg erythromycin tablet every 6 h for 7 consecutive days and two dummy tablets, identical in size and shape to dirithromycin, once daily for 5 days. Dirithromycin or its dummy was taken with or immediately after a meal. Erythromycin or its dummy was taken 1 h before meals and at bedtime. For each study, a centralized, treatment-balanced randomization table was produced and maintained electronically by the sponsor using the Almedica Drug Labeling System (ADLS). Blinded study-drug labels were produced for the medication kits and bottles. All investigators, participants and sponsor personnel involved in each study remained blinded to the randomization until the last patient had completed the protocol.

A II bottles with any remaining tablets were returned by the patient at the post-therapy visit and the remaining pills were counted. A patient was considered to be compliant if he or she returned ≥20% of the active drug dispensed.

Assessment of clinical efficacy

Patients were classified as clinically appraisable by a blinded investigator if they met the clinical inclusion and exclusion criteria and all data were collected.

To compare the efficacy of 5 days of dirithromycin with that of 7 days of erythromycin, clinical and bacteriological responses were assessed 3–5 (post-therapy) and 10–14 (late post-therapy) days after the completion of treatment. Clinical (symptomatic) response was assessed by the investigators as follows: cure: an elimination of signs and symptoms and no recurrence at the follow-up visits; improvement: a significant, but incomplete, resolution of signs or symptoms; relapse: worsening of signs and symptoms following an initial improvement; failure: no improvement. Patients were designated as unappraisable if they could not be assigned to a category and were disqualified for efficacy analysis.

Assessment of bacteriological efficacy

Patients were classified as bacteriologically appraisable by a blinded investigator if they had a positive culture of a pre-therapy sputum specimen with a respiratory pathogen. The following organisms were considered potential pathogens: H. influenzae, Klebsiella pneumoniae, S. pneumoniae, Klebsiella spp., M. catarrhalis, S. aureus, Haemophilus
parainfluenzae and streptococcus group A. Bacteriological response was based on microbiological culture data as follows: eradication: pathogen eliminated; persistence: culture positive for original pathogen; relapse: recurrence of the same pathogen with or without the development of resistance (required a positive follow-up culture preceded by at least one negative culture); colonization: culture positive for a new pathogen without the signs of infection; superinfection: culture positive for a new pathogen during therapy (required symptomatic response of failure or relapse); eradication with reinfection: culture positive for a new pathogen after treatment (required symptomatic response of failure or relapse).

If no follow-up sputum specimen was produced for culture, the following definitions were assigned: presumed microbiological persistence: no follow-up culture obtained with a symptomatic response of relapse or failure; presumptive eradication: implied absence of appropriate material for culture, or culture not clinically indicated (required symptomatic response of cure or improvement); indeterminate: could not be evaluated (bacteriological response could not be defined or categorized), or new antibiotic started for a condition other than the study indication before appropriate material for culture was obtained, or no pathogen isolated from the pre-therapy culture.

Assessment of safety

All adverse events occurring during the study were recorded. The frequency of adverse events was compared by treatment group and before and after each treatment. Adverse events were determined at each visit by questioning the patient and/or guardian regarding the occurrence and nature of any clinical adverse events. All patients or guardians were instructed to contact the investigator should the patient have any adverse events. A diverse events were classified using the US FDA Coding Symbol Thesaurus for Adverse Reaction Terms. Laboratory tests were compared between treatment groups and for an individual patient before and after receiving the drug.

Statistical methods

Sample sizes for both trials were determined by the method of Makuch & Simon. For each study, the planned sample size was 600 patients to obtain a minimum of 300 patients clinically appraisable (150 per treatment group). The true favourable response rates were 80% (case 1) or 90% (case 2) in both treatment groups, the sample size provided an 80% power of ruling out a difference of \( \geq 10\% \) (case 1) or \( \geq 10\% \) (case 2) with a two-sided 95% CI.

Efficacy results for the combined studies were analysed statistically by three subsets: (1) intent-to-treat analysis—patients randomized to each treatment group; (2) patients qualified for clinical analysis; (3) patients qualified for clinical and bacteriological analysis. Clinical efficacy was analysed for subgroups (1) and (2). Bacteriological efficacy was analysed for subgroups (1) and (3). Statistical analyses were performed on results at two time points: post-therapy, and termination or end of study. The termination analysis included patients who failed and discontinued at the post-therapy visit. Confidence intervals (CI) for the differences between proportions were constructed using the random effects model described by DerSimonian & Laird. The random effects model, a common meta-analysis method, makes no assumption about the constancy of the treatment effect and incorporates a measure of interstudy variability into the pooled estimate. Thus, the estimate of the treatment effect is a more conservative estimate with a wider confidence interval when heterogeneity is present.

For the statistical evaluation of safety results, all data from all patients entering the study were included. Chi-square tests were used to compare adverse event frequencies between treatment groups. Laboratory results were analysed by Student's t-tests to determine intra-group changes from baseline and by analysis of variance to determine changes between groups from baseline to the end of therapy.

Results

Patient characteristics and disposition

Between November 1991 and November 1992, 1057 outpatients from 77 principal investigators in North America were randomized to receive the study drug. Five hundred and thirty-one patients were randomized to receive dirithromycin and 526 patients were randomized to receive erythromycin. Demographic variables did not differ significantly between treatment groups (Table I). The distribution of age groups and ethnic origin was similar for the two treatment groups. A summary by treatment group of patient appraisability in the two studies and reasons for being clinically or bacteriologically unappraisable is shown in the Figure.

Clinical efficacy

Five days of dirithromycin was equivalent to 7 days of erythromycin in all measures of clinical response in treating acute exacerbations of chronic bronchitis at post-therapy and termination (Table II). Confidence intervals for the differences between the proportions of success in the two treatment groups contain zero indicating that there were no statistically significant differences between treatments. In each analysis, however, the point estimates of the differences favour dirithromycin-treated patients.

In the intent-to-treat group at post-therapy, 80% of the 531 dirithromycin-treated patients and 78.7% of the 526 erythromycin-treated patients had a favourable clinical outcome of cure or improvement. The 95% confidence
interval for the difference between proportions of favourable clinical responses was -3.7 to 6.0%, showing that the results of dirithromycin treatment were equivalent to those of erythromycin treatment (one can be 95% confident that dirithromycin given for 5 days for treatment of acute exacerbation of bronchitis is no worse than 3.7% less effective or may be as much as 6.0% better than erythromycin given for 7 days).

In the intent-to-treat group at termination, 74% of the 531 dirithromycin-treated patients and 71.5% of the 526 erythromycin-treated patients had favourable clinical outcomes. The 95% confidence interval for the difference in proportions of success was -2.8 to 7.8%, again confirming therapeutic equivalence between the two regimens.

In the group qualified for clinical evaluation, 84.2% of 354 dirithromycin-treated patients and 80.4% of 336 erythromycin-treated patients showed a successful clinical outcome at post-therapy (95% CI: -13.1 to 19.8%).

In the termination analysis of the group qualified for clinical evaluation, 77.1% of 354 dirithromycin-treated patients and 72.3% of 336 erythromycin-treated patients showed favourable clinical outcomes (95% CI: -9.1 to 17.9%).

### Bacteriological efficacy

The microbiological cure, as shown by sputum clearance or eradication of pathogen, of dirithromycin-treated patients was equivalent to that of those treated with erythromycin. In the intent-to-treat group at post-therapy, 47.8% of the 531 dirithromycin-treated patients and 48.5% of the 526 erythromycin-treated patients showed a favourable out-

### Table I. Demographic characteristics

<table>
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<tr>
<th>Demographic variable</th>
<th>Dirithromycin</th>
<th>Erythromycin</th>
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<tr>
<td>Number randomized</td>
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<td>526</td>
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<td>Female</td>
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<td>251</td>
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<td>Mean age (years)</td>
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<tr>
<td>12-&lt;21</td>
<td>16</td>
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<td>231</td>
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<td>50-&lt;65</td>
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<td>≥65</td>
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<td>127</td>
</tr>
<tr>
<td>Mean height (cm)</td>
<td>169.3</td>
<td>169.7</td>
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<tr>
<td>Mean weight (kg)</td>
<td>77.8</td>
<td>78.8</td>
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<tr>
<td>Ethnic origin</td>
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<td>3</td>
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<td>Black</td>
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<td>Caucasian</td>
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<tr>
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<td>0</td>
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<td>Other</td>
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<td>1</td>
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<tr>
<td>Smoking habit</td>
<td>243</td>
<td>255</td>
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### Figure. Summary of patient appraisability.
Dirithromycin therapy for chronic bronchitis

**Table II. Favourable clinical response**

<table>
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<th>Analysis subset</th>
<th>Intention-to-treat</th>
<th>Clinically appraisable</th>
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<tr>
<td></td>
<td>dirithromycin</td>
<td>erythromycin</td>
</tr>
<tr>
<td></td>
<td>post-therapy</td>
<td>termination</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Intention-to-treat study 1</td>
<td>206/249 (82.7)</td>
<td>208/250 (83.2)</td>
</tr>
<tr>
<td>study 2</td>
<td>219/282 (77.7)</td>
<td>206/276 (74.6)</td>
</tr>
<tr>
<td>total</td>
<td>425/531 (80.0)</td>
<td>414/526 (78.7)</td>
</tr>
<tr>
<td>95% CI*</td>
<td>(-3.7 to 6.0)</td>
<td>(-2.8 to 7.8)</td>
</tr>
<tr>
<td>Clinically appraisable study 1</td>
<td>133/164 (81.1)</td>
<td>137/159 (86.2)</td>
</tr>
<tr>
<td>study 2</td>
<td>165/190 (86.8)</td>
<td>133/177 (75.1)</td>
</tr>
<tr>
<td>total</td>
<td>298/354 (84.2)</td>
<td>270/336 (80.4)</td>
</tr>
<tr>
<td>95% CI*</td>
<td>(-13.1 to 19.8)</td>
<td>(-9.1 to 17.9)</td>
</tr>
</tbody>
</table>

*DerSimonian & Laird21 95% confidence interval for the difference between proportions of success (cure or improvement) for the two studies.

**Table III. Favourable bacteriological response**

<table>
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<th>Analysis subset</th>
<th>dirithromycin</th>
<th>erythromycin</th>
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<tr>
<td></td>
<td>post-therapy</td>
<td>termination</td>
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<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Intention-to-treat study 1</td>
<td>122/249 (49.0)</td>
<td>141/250 (56.4)</td>
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<tr>
<td>study 2</td>
<td>132/282 (46.8)</td>
<td>114/276 (41.3)</td>
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<tr>
<td>total</td>
<td>254/531 (47.8)</td>
<td>255/526 (48.5)</td>
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<tr>
<td>95% CI*</td>
<td>(-13.5 to 11.8)</td>
<td>(-11.3 to 13.1)</td>
</tr>
<tr>
<td>Bacteriologically evaluable study 1</td>
<td>76/103 (73.8)</td>
<td>88/108 (81.5)</td>
</tr>
<tr>
<td>study 2</td>
<td>102/125 (81.6)</td>
<td>82/108 (75.9)</td>
</tr>
<tr>
<td>total</td>
<td>178/228 (78.1)</td>
<td>170/216 (78.7)</td>
</tr>
<tr>
<td>95% CI*</td>
<td>(-14.0 to 12.2)</td>
<td>(-12.3 to 13.8)</td>
</tr>
</tbody>
</table>

*DerSimonian & Laird22 95% confidence interval for difference between proportions of success (cure or improvement) for the two studies.

The 95% confidence interval was –13.5 to 11.8%. Many patients in the dirithromycin and erythromycin treatment groups were not qualified for bacteriological evaluation due to a failure to isolate a pre-therapy pathogen (Figure).

In the intent-to-treat group at termination, 46.3% of the 531 dirithromycin-treated patients and 45.2% of the 526 erythromycin-treated patients showed favourable bacteriological outcomes (95% CI: –11.3 to 13.1%).

In patients qualified for bacteriological evaluation, at post-therapy, 78.1% of the 228 dirithromycin-treated patients and 78.7% of the 216 erythromycin-treated patients showed a successful bacteriological response (95% CI: –12.3 to 13.8%).

At termination, 75% of the 228 dirithromycin-treated patients showed successful bacteriological outcomes and 74.1% of the 216 erythromycin-treated patients showed successful bacteriological outcomes (95% CI: –12.3 to 13.8%).

When the results of treatment of patients infected by specific micro-organisms were analysed, dirithromycin was shown to be as effective as erythromycin in eradicating S. pneumoniae, H. influenzae, M. catarrhalis and S. aureus (Table IV).
Compliance

Dirithromycin-treated patients were statistically significantly more compliant than erythromycin-treated patients. Of the patients returning the bottles, 488 of 499 (97.8%) dirithromycin-treated patients were compliant whereas 438 of 504 (86.9%) erythromycin-treated patients were compliant (\(P\) 0.001).

Safety

There was no statistically significant difference between treatment groups in the proportions of patients reporting individual adverse events. Patients treated with dirithromycin, however, had fewer adverse events than those treated with erythromycin.

The most common adverse events for both dirithromycin-treated and erythromycin-treated patients were headache, abdominal pain, diarrhoea and nausea (Table V). Dirithromycin-treated patients reported fewer gastrointestinal adverse events (18.8%) than did erythromycin-treated patients (22.6%), although this finding was not statistically significant. Specifically, fewer dirithromycin-treated patients reported nausea, abdominal pain and diarrhoea than did erythromycin-treated patients. In addition, dirithromycin-treated patients (0.9%) had fewer discontinuations due to gastrointestinal adverse events than did erythromycin-treated patients (1.9%), although again this finding was not statistically significant.

Three (0.6%) dirithromycin-treated patients reported the common antibiotic side-effect of a rash, compared with seven (1.3%) erythromycin-treated patients. Eight (1.5%) dirithromycin-treated patients reported vaginitis, compared with four (0.8%) erythromycin-treated patients.

Serious adverse events were reported by nine dirithromycin-treated and 13 erythromycin-treated patients. Only one of these events (gastrointestinal haemorrhage experienced by a patient in the erythromycin-treated group) was thought to be possibly related to the study drug. One dirithromycin-treated patient was killed in an automobile accident 8 weeks after withdrawing from the study. This death was unrelated to study drug treatment.

Alterations in clinical laboratory tests, including blood chemistry, haematology and urinalysis, observed for dirithromycin-treated patients were similar to those for erythromycin-treated patients.

Discussion

Efficacy

Dirithromycin for 7-14 days has already been proved effective for acute exacerbations of chronic bronchitis, sec-
onydary bacterial infection of acute bronchitis, pharyngitis, tonsillitis, community-acquired pneumonia and skin infections. High tissue concentrations of erythromycin, the active metabolite of dirithromycin, and persistence of the drug in pulmonary tissues suggest a mechanism for the effectiveness of shorter duration of treatment. This meta-analysis of two identically designed, well-controlled, randomized clinical trials confirms the hypothesis that a shorter duration of dirithromycin treatment, 5 days, is effective in treating acute exacerbations of chronic bronchitis and that this dirithromycin treatment is therapeutically equivalent to 7 days of erythromycin. In patients with acute exacerbations of chronic bronchitis, dirithromycin for 5 days was also found to be as effective as 7 days of roxithromycin.

This study confirms the ability of dirithromycin to eradicate S. pneumoniae, H. influenzae, M. catarrhalis and S. aureus from the sputum of patients infected with these organisms (Table IV).

Although patients with bronchitis due to M. pneumoniae were not evaluated in this study, dirithromycin would be expected to treat bronchitis due to that organism, since it is effective for pneumonia due to M. pneumoniae.

Compliance
The improved compliance of the dirithromycin-treated patients may be due to the less frequent dosing of dirithromycin and fewer gastrointestinal adverse events. Additionally, dirithromycin-treated patients in this study had fewer discontinuations due to gastrointestinal adverse events than did erythromycin-treated patients.

Safety
Macrolides are generally safe antibiotics. The most common adverse events from macrolides are gastrointestinal, most commonly nausea, vomiting, abdominal pain and diarrhea. In this trial, dirithromycin had equivalent or fewer gastrointestinal adverse effects than erythromycin (Table V). Although these trials did not collect data on the frequencies of adverse events, the smaller proportion of dirithromycin-treated patients reporting gastrointestinal adverse events may be due to the less frequent dosing of dirithromycin. Furthermore, a lower rate of gastrointestinal events with dirithromycin may have contributed to the observed improvement in compliance among dirithromycin-treated patients, since patients with erythromycin-induced gastrointestinal adverse events may stop taking the drug. Additionally, the rates of adverse events from 5 days of dirithromycin were equivalent to or lower than those previously reported for 7–14 days of dirithromycin or erythromycin.

Dirithromycin compares favourably in the rate of common adverse events with other medications used for the treatment of bronchitis. Other adverse events or laboratory abnormalities reported with other macrolides and noted with dirithromycin in these studies include rash and elevated liver enzymes. Unlike erythromycin and clarithromycin, dirithromycin does not interact with the hepatic cytochrome P450 enzymes, thus lessening the interactions with drugs metabolized by the P450 enzymes. Specifically, dirithromycin does not interfere with the metabolism of terfenadine, cyclosporine, ethynyl oestradiol, or theophylline.

In summary, 5 days of dirithromycin is as effective as 7 days of erythromycin for acute exacerbations of chronic bronchitis. Dirithromycin has an improved or equivalent safety profile compared with erythromycin, exemplified by the trend to lower incidence of gastrointestinal adverse effects and the lack of interaction with cytochrome P450, which reduces the possibility of drug interactions.

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