Pergamon

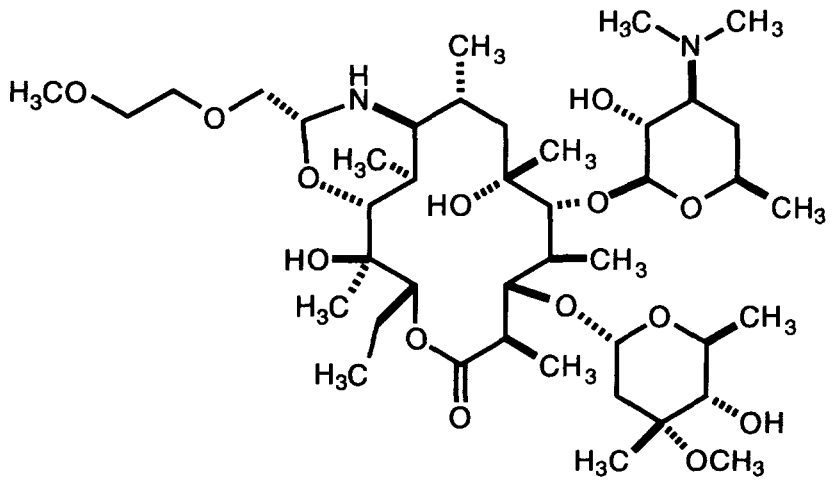
Bioorganic & Medicinal Chemistry, Vol. 4, No. 4, pp. 521–522, 1996

0968-0896/96 $15.00 + 0.00

S0968-0896(96)00052-1

New Drugs—Reports of New Drugs Recently Approved by the FDA

Dirithromycin



Structure
$C_{42}H_{78}N_2O_{14}$

[9S(*R*)]-9-Deoxy-11-deoxy-9,11-[imino[2-(2-methoxyethoxy)ethylidene]oxo]erythromycin
[CAS 62013-04-1]

Supply: Crystals from ethanol/water, mp 186–189 °C (dec); $pK_a = 9.0$.

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Mechanism of action: The mechanism of action of dirithromycin is like that of erythromycin and other macrolides. Dirithromycin binds reversibly to the 23S component of the 50S ribosomal subunit, inhibiting RNA-dependent protein synthesis.

Therapeutic category: Antibiotics; Antimicrobials.

Synthesis: Dirithromycin is synthesized by cyclocondensation of 9-(*S*)-erythromycylamine and 2-(2-methoxyethoxy)-acetaldehyde.[1]

Summary: Dirithromycin is a semisynthetic derivative of erythromycin, a 14-membered ring macrolide antibiotic. The drug is converted during absorption and distribution, to an active metabolite 9-(*S*)-erythromycylamine, which is the predominant compound found in plasma and extravascular tissues. High tissue concentration of erythromycylamine is achieved after oral doses of dirithromycin, with slow release back into the circulation.[1] The mechanism of action of dirithromycin is like that of erythromycin and other macrolides. These compounds inhibit RNA-dependent protein synthesis.[1–3] It has recently been suggested that all macrolides stimulate dissociation of peptidyl-tRNA from ribosomes during the elongation phase, leading to inhibited protein synthesis.[2] The antimicrobial spectrum of dirithromycin is similar to that of erythromycin, although the drug offers no significant advantage with regard to MIC values. In vitro against Gram-positive isolates, dirithromycin exhibits similar potency to that of clarithromycin, erythromycin, roxithromycin, and clindamycin. In vivo, dirithromycin is active against

penicillin-susceptible *Staphylococcus aureus*, beta-hemolytic streptococci, and *Streptococccus pneumoniae*. Dirithromycin is as effective as penicillin VK against streptococcal pharyngitis and tonsilitis, and as effective as erythromycin against acute superimposed chronic bronchitis and skin and soft-tissue infections. In comparison with other newer macrolides, dirithromycin has shown similar or lesser in vitro activity. In particular, *Haemophilus influenzae*, *Bacteroides* spp., *Peptococcus-Peptostreprococcus* spp., *Clostridium perfringens*, *Legionella* spp., *Neisseria gonorrhoeae*, and *Chlamydia trachomatis* were all less sensitive to dirithromycin than azithromycin or clarithromycin.[3,4] Once-daily oral administration of dirithromycin (500 mg) has been demonstrated to be similar in efficacy to erythromycin (250 mg, 4 times daily), each for approximately 7 days, in the treatment of acute bronchitis or acute exacerbations of chronic bronchitis in controlled studies.[1,3] Proven or presumed pathogen eradication rates were 83 and 86% for acute bronchitis patients treated with dirithromycin and erythromycin, respectively. Corresponding bacteriological response rates in acute exacerbations of chronic bronchitis were 75 to 84% with dirithromycin and 75 to 82% with erythromycin. Both agents achieved clinical cure or improvement in over 85% of the patients with either condition. The main advantage of dirithromycin over erythromycin appears to be once-daily administration. Lilly launched dirithromycin in September 1993, in Spain, received approval from the FDA in August 1995, and launched it during October 1995.

Manufacturer: Lilly (U.S.A.).

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