Nominations from FDA's Center for Drug Evaluation and Research

Genotoxicity and Carcinogenicity Testing of Clarithromycin (CDER)

Clarithromycin is a semi-synthetic macrolide antibiotic. Chemically, it is 6-O-methylerythromycin with a molecular formula of $C_{38}H_{69}NO_{13}$. It is absorbed from the gastrointestinal tract after oral administration but only about 50% became bioavailable. The reactive metabolite is 14-OH Clarithromycin. Peak serum levels were achieved in two hours in adults with steady state reached in 2 – 3 days.

Clarithromycin tablets and Clarithromycin granules for oral suspension are indicated for the treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the following conditions: 1) Pharyngitis/Tonsillitis due to Streptococcus pyrogenes (the usual drug of choice in the treatment and prevention of streptococcal infections and the prophylaxis of rheumatic fever is penicillin administered by either the intramuscular or the oral route. Clarithromycin is generally effective in the eradication of Streptococcus pyrogenes from the nasopharynx; however, data establishing the efficacy of Clarithromycin in the subsequent prevention of rheumatic fever are not available at present.); 2) Acute Maxillary Sinusitis due to Haemophilus influenzae, Moraxella catarrhalis, or Streptococcus pneumoniae; 3) Acute Bacterial Exacerbation of Chronic Bronchitis due to Haemophilus influenzae, Moraxella catarrhalis, or Streptococcus pneumoniae; 4) Pneumonia due to Mycoplasma pneumoniae, Streptococcus pneumonia, or Chalmydia pneumoniae; 5) Uncomplicated skin and skin structure infections due to Staphylococcus Aures, or Staphlococcus pyrogenes; and 6) Disseminated Mycobacterial Infections due to Mycobacterium avium and Mycobacterium intercellulare.

Clarithromycin (in combination with omeprazole or anitidine bismuth citrate) is indicated for the treatment of patients with an active duodenal ulcer associated with Helicobacter pylori infection.

The recommended dose of Clarithromycin for the prevention of disseminated Mycobacterium avium disease is 500 mg b.i.d. In children, the recommended dose is 7.5 mg/kg b.i.d. up to 500 mg b.i.d. No studies of Clarithromycin for MAC prophylaxis have been performed in pediatric populations and the doses recommended for prophylaxis are derived from Mycobacterium Avium Complex (MAC) treatment studies in children. Clarithromycin is recommended as the primary agent for the treatment of disseminated infection due to MAC. Clarithromycin should be used in combination with other anti-mycobacterial drugs that have shown *in vitro* activity against MAC, including ethambutol, clofazimine, and rifampin. The recommended dose for mycobacterial infections in adults is 500 mg b.i.d. In children, the recommended dose is 7.5 mg/kg b.i.d. up to 500 mg b.i.d. Clarithromycin therapy is recommended to continue for life if clinical and mycobacterial improvements are observed.

Hepatotoxicity (rats, dogs, and monkeys), renal tubular degeneration (rats, dogs, and monkeys), testicular atrophy (rats, dogs, and monkeys), and lymphoid depletion (rats,

dogs, and monkeys) have been observed in studies reported to the FDA. No chronic cancer studies have been conducted, and CDER is requesting such a study because of the rapid absorption and distributed of the drug into body tissues and fluids and the current use patterns.