CHLOROMYCETIN® FOR ORAL ADMINISTRATION

(CHLORAMPHENICOL, PARKE, DAVIS & COMPANY)

WARNING

Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after short term and with prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective, or in the treatment of trivial infections such as colds, influenza, viral infections of the throat, or as a prophylactic agent.

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied upon to detect bone marrow depression prior to development of aplastic anemia.

Chloramphenicol is a broad-spectrum antibiotic which clinical experience has shown to have specific therapeutic activity against a wide variety of organisms. Its activity was demonstrated initially in culture filtrates from a species of soil organism collected in Venezuela, later designated as *Streptomyces venezuelae*. The antibiotic was subsequently isolated from culture filtrates, identified chemically and later synthesized.

Experimental development of bacterial resistance to chloramphenicol by staphylococci *in vitro* occurs comparatively slowly and only to a moderate degree. Strains of decreased susceptibility to chloramphenicol are relatively short-lived both *in vitro* and in man. In a survey of experimental and clinical experiences on susceptibility of staphylococci to chloramphenicol, it was found that the incidence of chloramphenicol-resistant staphylococci appears unrelated to frequency or to intensity of use of this antibiotic. Development of resistance to chloramphenicol can be regarded as minimal for staphylococci and many other species of bacteria.

ANTIMICROBIAL AND PHARMACOLOGICAL PROPERTIES OF CHLORAMPHENICOL

Chloramphenicol is absorbed rapidly from the intestinal tract, producing detectable concentrations in blood within one-half hour after administration and peak concentration in from 1 to 3 hours. Peak blood concentration is roughly proportional to the dose. Following absorption of the drug and attainment of equilibrium conditions with body fluids and tissues, concentration in blood falls approximately 50 per cent in succeeding 3- to 4-hour periods. **Chloromycetin Palmitate** requires enzymatic hydrolysis to chloramphenicol before absorption. Resulting blood concentration is similar to that produced by the oral administration of chloramphenicol.

Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. This antibiotic has also been reported to occur in pleural and in ascitic fluids, saliva, and in milk, and it diffuses readily into all parts of the eye. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

Seventy to ninety per cent of a single oral dose of 50 mg. of chloramphenicol is excreted in 24 hours in the urine of human subjects, with 5 to 10 per cent as free chloramphenicol and the remainder as microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most nitro compounds in the blood are in the form of free chloramphenicol. Despite the small proportion of unchanged drug excreted in the urine, concentrations therein are relatively high, amounting to several hundred mcg./ml., in patients receiving divided doses of 50 mg./kg./day. Small amounts of the drug are also found in bile and in feces.

DOSAGE RECOMMENDATIONS FOR ORAL CHLOROMYCETIN PRODUCTS

The majority of microorganisms susceptible to chloramphenicol will respond to a concentration between 5 and 20 mcg./ml. The desired concentration of active drug in blood should fall within this range over a major portion of the treatment period. Dosage of 50 mg./kg./day divided into 4 doses at intervals of 6 hours will achieve levels of this magnitude. Except in certain circumstances (e.g., premature and newborn infants) lower doses may not achieve these concentrations. Chloramphenicol, like other potent drugs, *must* be prescribed at recommended doses known to have therapeutic activity. The following recommendations apply to all oral preparations: