1.0 THERAPEUTIC CATEGORY
Antibacterial

2.0 DESCRIPTION

**Chloramphenicol sodium succinate**
(1g Lyophilized Powder for Injection)

Chloramphenicol (succinate) is an antibiotic originally isolated from *Streptomyces venezuelae*. Its chemical name is sodium (2R,3R)-2-(2,2-Dichloroacetamido)-3-hydroxy-3-(4-nitrophenyl) propyl succinate, C_{15}H_{15}Cl_{2}N_{2}NaO_{8} (MW = 445.2). The structure of chloramphenicol is:

![Structure of Chloramphenicol](image)

Chloramphenicol sodium succinate occurs as a white to light yellow powder, and is freely soluble in water and in alcohol. Each gram (10 mL of a 10% solution) of chloramphenicol sodium succinate contains approximately 2.25 mEq (52 mg) of sodium.

**Chloramphenicol / Chloramphenicol palmitate**
(Capsule and Suspension)

Chloramphenicol/chloramphenicol (palmitate) is an orally active antibiotic originally isolated from *Streptomyces venezuelae*. The chemical name for chloramphenicol palmitate is (2R,3R)-2-(2,2-dichloroacetamido)-3-hydroxy-3-(4-nitrophenyl) propyl palmitate, C_{27}H_{42}Cl_{2}N_{2}O_{6} (MW = 561.5). The structure for chloramphenicol is:

![Structure of Chloramphenicol Palmitate](image)

Chloramphenicol occurs as fine, white to grayish or yellowish white, needle-like crystals, has a solubility of approximately 2.5 mg/mL in water at 25°C, and is freely soluble in alcohol. The pKₐ of the drug is 5.5. Chloramphenicol palmitate occurs as a fine, white, unctuous, crystalline powder having a faint odor and a bland mild taste and is insoluble in water and sparingly soluble in alcohol.
3.0 FORMULATION

Chloromycetin 250 mg Capsule: Each capsule contains 250 mg chloramphenicol.
Chloromycetin 500 mg Capsule: Each capsule contains 500 mg chloramphenicol.
Chloromycetin Suspension: Each 5 mL contains chloramphenicol palmitate equivalent to 125 mg chloramphenicol
Chloromycetin Lyophilized Powder for Injection: When reconstituted with sterile water for injection, each vial will contain a sterile solution of chloramphenicol sodium succinate equivalent to 200 mg of chloramphenicol per mL

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Chloramphenicol is an antibiotic that is clinically useful for, and should be reserved for, serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. However, chloramphenicol may be chosen to initiate antibiotic therapy on the clinical impression that one of the conditions listed below is believed to be present. In vitro sensitivity tests should be performed concurrently so that the drug may be discontinued as soon as possible if less potentially dangerous agents are indicated by the results of such tests.

The decision to continue use of chloramphenicol, rather than another antibiotic when both are suggested by in vitro studies to be effective against a specific pathogen, should be based upon severity of the infection, susceptibility of the pathogen to the various antimicrobial drugs, and the efficacy of the various drugs in the infection. (See section 4.4 Special Warnings and Special Precautions for Use)

1) Acute infections caused by *Salmonella typhi*
   Chloramphenicol is a drug of choice.* It is not, however, recommended for the routine treatment of the typhoid carrier state.

2) Serious infections caused by susceptible strains in accordance with the concepts expressed above:
   a. *Salmonella* species
   b. *Haemophilus influenzae*, specifically meningeval infections
   c. *Rickettsia*
   d. *Lymphogranuloma-psittacosis group*
   e. Various gram-negative bacteria causing bacteremia, meningitis or other serious gram-negative infections

* In the treatment of typhoid fever, some authorities recommend that chloramphenicol be administered at therapeutic doses for 8 to 10 days after the patient has become afebrile to lessen the possibility of relapse.
f. Other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents.

3) Cystic fibrosis regimens

4.2 Dosage and Method of Administration Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Inhibition of the majority of sensitive organisms may be expected at concentrations of 5 to 20 mcg/mL. The desired serum concentration of active drug should fall within this range over most of the treatment period. Dosages of 50 mg/kg/day divided into 4 doses and administered at 6 hour intervals will usually achieve and sustain levels of this order.

Except in certain circumstances (e.g., premature infants, neonates, and in patients with hepatic or renal impairment), lower doses may not achieve these concentrations. Close observation of the patient should be maintained and in the event of any adverse reactions, the dosage should be reduced or the drug discontinued, if other factors in the clinical situation permit.

Parenteral

Injectable chloramphenicol sodium succinate is intended for intravenous (IV) use. Intramuscular (IM) administration results in lower serum levels, which may be ineffective. The use of the IM route should be restricted to those patients where oral dosing is not possible, and IV use is impossible or impractical. Accordingly, higher than the recommended dosage of the succinate should be considered when it is administered IM.

Intravenous
50 mg/kg/day in divided doses at 6 hour intervals will produce serum levels of the magnitude to which the majority of susceptible microorganisms will respond.

Intramuscular
75 mg/kg/day in divided doses at 6 hour intervals in order to achieve desired serum levels.

As soon as feasible, an oral dosage form of chloramphenicol should be substituted for the parenteral form because adequate serum levels are achieved with chloramphenicol when administered by mouth.
The following method of administration is recommended: Intravenously as a 10% (100 mg/mL) solution to be injected over a period of about a minute, or in a larger volume of fluid, by slow intravenous infusion. (See section 6.3 Instructions for Use and Handling)

**Parenteral and Oral**

**Use in Adults**
Adults should receive 50 mg/kg/day (approximately one 250 mg capsule per each 4.5 kg (10 lbs.) of body weight) in divided doses at 6 hour intervals. In exceptional cases, patients with infections due to moderately resistant organisms may initially require increased dosages of up to 100 mg/kg/day to achieve serum levels which inhibit the pathogen, but these high doses should be decreased as soon as possible. Adults with impaired hepatic or renal function, or both, may have reduced ability to metabolize and excrete the drug.

In instances of impaired metabolic processes, dosages should be adjusted accordingly.

**Use in Pediatric Patients**
A dosage of 50 mg/kg/day in divided doses at 6 hour intervals is effective against most susceptible organisms. Severe infections (e.g. bacteremia or meningitis), when adequate cerebrospinal fluid drug levels are desired, may require dosages of up to 100 mg/kg/day; however, it is recommended that dosages be reduced to 50 mg/kg/day as soon as possible.

Pediatric patients with impaired hepatic or renal function may retain excessive amounts of the drug.

**Use in Neonates**
A total of 25 mg/kg/day in 4 equal doses at 6 hour intervals usually produces and maintains concentrations in serum and tissues adequate to control most infections for which the drug is indicated. These dosage recommendations are extremely important because serum concentration in all premature neonates and full-term neonates less than two weeks of age differs from that of other infants. (See section 4.2 Dosage and Method of Administration – Use in Pediatric Patients with Immature Metabolic Processes) This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.

Increased dosages in these patients, demanded by severe infections, should be given only to maintain the serum concentration within a therapeutically effective range. After the first two weeks of life, full-term neonates ordinarily may receive up to a total of 50 mg/kg/day, equally divided into 4 doses at 6 hour intervals.
When these functions are immature (or seriously impaired in adults), high serum concentrations of the drug are found which tend to increase with succeeding doses. (See section 4.4 Special Warnings and Special Precautions for Use – Gray Syndrome)

**Use in Pediatric Patients with Immature Metabolic Processes**

In young infants and other pediatric patients in whom immature metabolic functions are suspected, a dose of 25 mg/kg/day will usually produce therapeutic serum concentrations of the drug. In these patients particularly, the serum drug concentration should be carefully monitored by microbiological techniques where possible.

**4.3 Contraindications**

Chloramphenicol is contraindicated in individuals with known hypersensitivity and/or toxic reaction to the product or its components.

**4.4 Special Warnings and Special Precautions for Use**

**Hematologic Effects**

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia, and bone marrow depression) are known to occur after the administration of chloramphenicol. (See section 4.8 Undesirable Effects) In addition, there have been reports of aplastic anemia attributed to chloramphenicol, which later resulted in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective.

It is essential that adequate hematologic functions be closely monitored during treatment with chloramphenicol. While hematologic determinations may detect early peripheral hematologic changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such determinations cannot be relied on to detect bone marrow depression prior to the development of aplastic anemia.

It is desirable that patients be hospitalized during therapy, so that appropriate laboratory determinations and clinical observations can be made.

Baseline hematologic determinations should be made and determinations repeated approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or any other hematologic findings attributable to chloramphenicol. However, such determinations do not exclude the possible later appearance of the irreversible type of bone marrow depression.

Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk of relapse of the disease.
Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.

**Hepatic or Renal Impairment**

Excessive chloramphenicol serum levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. Dosage should be adjusted accordingly or, preferably, the serum concentration should be determined at appropriate intervals. (See section 4.2 Dosage and Method of Administration)

**Gray Syndrome**

Precaution should be used in therapy of premature and full-term neonates to avoid "Gray Syndrome" toxicity. Serum drug levels should be carefully monitored during therapy of the neonate (newborn infant).

Toxic reactions, including fatalities, have occurred in premature infants and neonates. The signs and symptoms associated with these reactions have been referred to as the "Gray Syndrome". Although "Gray Syndrome" has been reported in neonates born to mothers after having received chloramphenicol during labor, in most cases therapy with chloramphenicol has been instituted within the first 48 hours of life. The following summarizes the clinical and laboratory determinations that have been made on these patients.

Symptoms first appeared after 3 to 4 days of continued treatment with high doses of chloramphenicol. The symptoms appeared in the following order: abdominal distension with or without emesis, progressive pallid cyanosis, vasomotor collapse, frequently accompanied by irregular respiration, death within a few hours of onset of these symptoms. The progression of symptoms from onset to death was accelerated with higher dose schedules. Serum drug levels revealed unusually high concentrations of chloramphenicol (over 90 mcg/mL after repeated doses).

Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery following.

**General**

Chloramphenicol must not be used in the treatment of trivial infections or where it is not indicated, as in colds, viral influenza, infections of the throat or as a prophylactic agent to prevent bacterial infections.

The use of chloramphenicol, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including chloramphenicol, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C difficile.*

3-16
C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.3-16

4.5 Interactions with Other Medicaments and Other Forms of Interaction

Chloramphenicol has been shown to retard the biotransformation of tolbutamide, phenytoin, and dicoumarol in man. Chloramphenicol should be used with caution if administered concomitantly with lincomycin, clindamycin, or erythromycin. In vitro experiments have demonstrated that binding sites for erythromycin, lincomycin, clindamycin and chloramphenicol overlap and competitive inhibition may occur. Rifampin therapy can reduce chloramphenicol concentrations.

Chloramphenicol has been shown to increase serum concentrations of tacrolimus when these drugs are administered concurrently. Dose reductions and careful monitoring of tacrolimus levels are recommended to avoid toxicity.

4.6 Pregnancy and Lactation

There are no studies to establish the safety of this drug in pregnancy.

Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus. (See section 4.4 Special Warnings and Special Precautions for Use – Gray Syndrome)

Chloramphenicol is excreted in breast milk. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant (e.g. Gray Syndrome, bone marrow suppression).

4.7 Effects on Ability to Drive and Use Machines

The effect of chloramphenicol on the ability to drive or use machinery has not been systematically evaluated. There is no evidence to suggest that this drug may affect these abilities.

4.8 Undesirable Effects

Blood and Lymphatic System Disorders: (See section 4.4 Special Warnings and Special Precautions for Use – Hematologic Effects).

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance, weeks or months after therapy, of bone
marrow aplasia or hypoplasia. Peripherally, pancytopenia is observed most often, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed. A dose related reversible type of bone marrow depression may occur.

This type of marrow depression which is characterized by vacuolization of the erythroid cells, and reduction of reticulocytes and leukopenia, responds promptly to the withdrawal of chloramphenicol.

Paroxysmal nocturnal hemoglobinuria has also been reported.

**Immune System Disorders:** anaphylaxis, Herxheimer reactions have occurred during therapy for typhoid fever.

**Psychiatric Disorders:** delirium, mental confusion, mild depression

**Nervous System Disorders:** headache, peripheral neuritis usually following long-term therapy (if this occurs, the drug should be promptly withdrawn).

**Eye Disorders:** optic neuritis usually following long-term therapy (if this occurs, the drug should be promptly withdrawn).

**Gastrointestinal Disorders:** nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

**Cardiac Disorders:** Gray Syndrome (See section 4.4 Special Warnings and Special Precautions for Use – Gray Syndrome)

**Skin and Subcutaneous Tissue Disorders:** angioedema, macular and vesicular rashes, urticaria

**General Disorders and Administration Site Conditions:** fever

### 4.9 Overdose

Levels exceeding 25 mcg/mL are frequently considered toxic. Chloramphenicol toxicity can be evidenced by serious hemopoietic effects such as aplastic anemia, thrombocytopenia, leukopenia, as well as increasing serum iron levels, nausea, vomiting and diarrhea. In the case of serious overdosage, charcoal hemoperfusion may be effective in removing chloramphenicol from plasma.

Exchange transfusion is of questionable value following massive overdosage, especially in neonates and infants.

### 5.0 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic Properties

*In vitro*, chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is active against rickettsiae, the lymphogranuloma-psittacosis group and *Vibrio cholerae*. It is particularly active against *Salmonella typhi* and *Haemophilus influenzae*. The mode of action is via interference with or inhibition of protein synthesis in intact cells and cell-free systems.

5.2 Pharmacokinetic Properties

Interindividual variation exists in determining the pharmacokinetics for a given patient with impaired and/or immature hepatic or renal function. (See section 4.2 Dosage and Method of Administration)

**Absorption**

Chloramphenicol sodium succinate must be hydrolyzed to its microbiologically active form and there is a lag in achieving adequate serum levels compared with the base given intravenously. The oral form of chloramphenicol is readily absorbed and adequate serum levels are achieved and maintained on the recommended dosage. Chloramphenicol is rapidly absorbed from the GI tract. Chloramphenicol palmitate is hydrolyzed in the GI tract and is absorbed as free chloramphenicol.

Following parenteral administration, cumulative dosing gave a peak of 18 mcg/mL every 6 hours. Following oral administration of a single one gram dose of chloramphenicol base to healthy adults, average peak plasma chloramphenicol concentrations of about 11 mcg/mL were attained within 1-3 hours. Cumulative dosing gave a peak of 18 mcg/mL after the fifth dose of one gram, every 6 hours. Mean serum levels were 8-14 mcg/mL over a 48 hour period for both parenteral and oral formulations.

**Distribution**

Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in the brain and cerebrospinal fluid (CSF). Chloramphenicol enters CSF even in the absence of meningeal inflammation, appearing in concentrations of about half those found in the blood.

**Metabolism**

Chloramphenicol is inactivated primarily in the liver by glucuronyl transferase.

**Elimination**

In adults with normal renal and hepatic function, most of the drug is excreted in the urine. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol in the urine is relatively high. From 8% to 12% is excreted as free chloramphenicol. A higher proportion (30%) is excreted unchanged following intravenous administration. The remainder is excreted as inert metabolites, mainly glucuronate. Small amounts of active drug are found in bile and feces following oral administration.
6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf Life
See outer package for the expiry date of the product.

6.2 Storage Condition

Chloramphenicol palmitate oral suspension should be stored at temperatures not exceeding 30°C. It should be protected from freezing.

Chloramphenicol capsules should be stored at temperatures not exceeding 30°C. They should be protected from moisture and excessive heat.

Chloramphenicol sodium succinate sterile powder should be stored at a temperature not exceeding 25°C. When reconstituted as directed, the solution is stable for 30 days at room temperature. Cloudy solutions of chloramphenicol succinate should not be used.

6.3 Instructions for Use and Handling

Parenteral

Chloramphenicol 20% (200 mg/mL) solution is prepared by the addition of 4.2 mL of an aqueous diluent, such as water for injection or 5% dextrose injection. The 10% solution can be prepared by extracting 5ml of the 20% solution and adding 5ml of diluent (Water for Injections, Sodium Chloride Injection, or Dextrose Injection 5%) under aseptic conditions.

6.4 Availability

Chloromycetin Palmitate Suspension - a white opaque suspension with a vanilla-custard odor, free from visible contaminants. Supplied in bottles of 30 and 60 mL.

Chloromycetin 250 mg Capsules – hard gelatine capsules with white opaque body and light gray cap imprinted in black with Chloro 250 mg and Parke Davis, containing a white powder. Supplied in blisterpack of 20’s x 10 per box.

Chloromycetin 500 mg Capsules – hard gelatine capsule with light gray opaque cap, white opaque body and imprinted in black with Chloro 500 mg and Parke Davis, containing a white powder. Supplied in blisterpack of 20’s x 10 per box.

Chloramphenicol sodium succinate is supplied as lyophilized powder for injection in sterile rubber diaphragm-capped vials.

CAUTION: Food, Drug, Devices, and Cosmetics Act prohibits dispensing without prescription.
REFERENCES


