PRESCRIBING INFORMATION
PRODUCT MONOGRAPH

CHLOROMYCETIN* SUCCINATE INJECTION

(Chloramphenicol Sodium Succinate for Injection Ph.Eur)

(Equivalent to 1g chloramphenicol per vial)
For Intravenous Use

Antibiotic

ERFA Canada 2012 Inc.

8250 Décarie Blvd, suite 110
Montréal, QC
Canada, H4P 2P5

DATE OF PREPARATION: 16-Aug-2005

DATE OF REVISION:

CONTROL NUMBER: 100443

PRESCRIBING INFORMATION

CHLOROMYCETIN* SUCCINATE INJECTION

(Chloramphenicol Sodium Succinate for Injection PH.EUR)

(Equivalent to 1g chloramphenicol per vial)
For Intravenous Use

THERAPEUTIC CLASSIFICATION

Antibiotic

ACTIONS AND CLINICAL PHARMACOLOGY

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 lymphogranulomapsittacosis group and *Vibrio cholerae*. It is particularly active against *Salmonella typhi* and *Haemophilus influenzae*. The mode of action is through interference or inhibition of protein synthesis in intact cells and cell-free systems.

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract producing detectable concentrations in blood within one half-hour after administration and peak concentration in from ½ to 3 hours. The peak blood concentration is roughly proportional to the dose. Following the absorption of the drug and attainment of equilibrium conditions with body fluids and tissues, the concentration in blood falls approximately 50% in the succeeding 3 to 4 hour period.

Chloramphenicol sodium succinate requires conversion to free chloramphenicol before exhibiting significant antimicrobial activity. When given intravenously peak concentrations of free chloramphenicol are reached quickly.

Following intramuscular injection, serum levels are lower and peak levels occur later than following either oral or intravenous administration. Therefore the intramuscular route is not recommended.

Chloramphenicol sodium succinate is intended for intravenous use only and patients should be changed to oral therapy as soon as practicable.

Chloramphenicol diffues rapidly, but its distribution is not uniform. Highest concentrations are found in the liver and kidney, and lowest concentrations are found in the brain and cerebrospinal fluid. Chloramphenicol enters the cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half that found in the blood. This antibiotic has also been reported to occur in pleural and in ascitic fluids, saliva and in milk, and it diffues 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.

INDICATIONS AND CLINICAL USE

Chloramphenicol must not be used in the treatment of trivial infections.

In accordance with the concepts in the 'Warning' and this Indications section, chloramphenicol should be used only in those conditions for which it may be the antibiotic of choice. These would include:

1. Acute infections caused by *Salmonella typhi*. It is not recommended for the routine treatment of the typhoid 'carrier' state.

2. Serious infections caused by susceptible strains:

   (a) *Salmonella* species with systemic involvement.
   (b) *H. influenzae*, specifically meningeal infections.
   (c) *Rickettsia*; psittacosis in children.
   (d) Various Gram-negative bacteria causing bacteremia, meningitis or other serious Gram-negative infections.
   (e) Other susceptible organisms which have been demonstrated to be resistant to other appropriate antimicrobial agents.

3. Cystic fibrosis regimens.

CONTRAINDICATIONS

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reaction to it.

WARNINGS

Serious and fatal blood dyscrasias (aplastic anemia, bone marrow hypoplasia, thrombocytopenia, granulocytopenia) have been reported with the use of chloramphenicol. It is essential that adequate blood studies be done.

Chloramphenicol must not be used in the treatment or prophylaxis of minor infections, or where it is not indicated, as in colds, influenza, or infections of upper respiratory tract. There are two types of bone marrow depression associated with the use of chloramphenicol. Some degree of depression of the bone marrow is commonly seen during therapy, is dose related and is potentially reversible; blood studies may detect early changes. The other is very rare, a sudden, delayed and usually fatal bone marrow hypoplasia which may occur without warning.

PRECAUTIONS

1. It is essential that appropriate blood studies be made during treatment with chloramphenicol. While blood studies may detect early peripheral blood changes, such studies cannot be relied on to detect the rare and generally irreversible bone marrow depression prior to development of aplastic anemia.

2. Baseline blood studies should be followed by periodic blood studies at intervals during therapy. Dependent upon the severity of the disease being treated, the drug may be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or other blood alterations attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.

3. 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.

4. Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.

5. Excessive blood 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. The dosage should be adjusted accordingly and the blood concentration should be determined at appropriate intervals, if possible.

6. Caution should be used in therapy of premature and full-term infants to avoid 'gray syndrome' toxicity (see Adverse Reactions). Serum drug levels should be carefully followed during therapy of the neonate.

7. There are no studies which establish the safety of this drug for use in pregnancy. Benefit to the mother must be weighed against a possible risk to the fetus. Use of the drug at term or during labor may pose an additional hazard to the fetus since chloramphenicol readily crosses the placental barrier. One case of 'gray syndrome' has been reported in a neonate born to a mother having received chloramphenicol intravenously during labor.

8. The use of this antibiotic, as with other antibiotics, may result in the overgrowth of nonsusceptible organisms, including fungi.

ADVERSE REACTIONS

1. **Blood Dyscrasias:** 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 rarely after the administration of chloramphenicol. A generally 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 most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may

   be depressed. There have been reports of aplastic anemia attributed to chloramphenicol later terminating in leukemia.

A reversible type of bone marrow depression which is dose related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes and leukopenia, and responds to withdrawal of chloramphenicol.

Paroxysmal nocturnal hemoglobinuria has also been reported.

2. **Gastrointestinal Reactions:** Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

3. **Neurotoxic Reactions:** Headache, mild depression, mental confusion and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly discontinued.

4. **Hypersensitivity Reactions:** Fever, macular and vesicular rashes, angioedema, urticaria and anaphylaxis may occur.

   The Herxheimer reaction has occurred during therapy for typhoid fever.

5. **'Gray Syndrome':** Toxic reactions including fatalities have occurred in the premature and newborn age group. The signs and symptoms associated with these reactions have been referred to as the 'gray syndrome'. The following summarizes the clinical and laboratory studies that have been made on these patients.

   In most cases therapy with chloramphenicol had been instituted within the first 48 hours of life.

   Symptoms first appeared after 3 to 4 days of continued treatment with high doses of chloramphenicol.

   The symptoms appeared in the following order:

   (a) abdominal distention with or without emesis;
   (b) progressive pallid cyanosis;
   (c) vasomotor collapse frequently accompanied by irregular respiration;
   (d) death within a few hours of onset of these symptoms.

The progression of symptoms from onset to death was accelerated with higher dose schedules.

Blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 μg/mL) after repeated doses.

Termination of therapy upon early evidence of the associated symtomatology frequently revised the process with complete recovery.

6. Chloramphenicol has been shown to retard the biotransformation of tolbutamide, phenytoin, and dicumarol in man.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Levels exceeding 25 μg/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.

DOSAGE AND ADMINISTRATION

Chloramphenicol must be prescribed in adequate dosage. Inhibition of the majority of sensitive organisms may be expected at blood levels of 5 to 20 μg/mL. Levels of the order of 10 μg/mL are usually achieved following oral doses of 50 mg/kg daily.
Where possible, chloramphenicol should be administered orally. Consequently, patients started on intravenous chloramphenicol sodium succinate should be changed to the oral form as soon as practicable.

Adults
Adults should receive 50 mg/kg/day in divided doses at 6-hour intervals. In exceptional cases patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg/kg/day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible.

Adults with impairment of 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 (see discussion under 'Newborn Infants').

Children

Dosage of 50 mg/kg/day divided at 6-hour intervals is effective against most susceptible organisms. Severe infections (e.g. septicemia or meningitis) especially when adequate cerebrospinal fluid concentrations are desired, require dosage up to 100 mg/kg/day divided at 6 or 12 hour intervals. It is recommended that dosage be reduced to 50 mg/kg/day as soon as possible.

Children with impaired liver or kidney functions or both may retain excessive amounts of the drug.

Newborn Infants
(Premature and Full-Term)

For newborn infants a total of 25 mg/kg/day in 4 equal doses at 6-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these individuals demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first 2 weeks of life, full term infants ordinarily may receive up to a total of 50 mg/kg/day equally divided into 4 doses at 6-hour intervals. **These dosage recommendations are extremely important because blood concentration in all premature infants and full term infants under 2 weeks of age differs from that of other infants.** This difference is due to variations in the maturity of the metabolic functions of the liver and kidneys.

When these functions are immature (or seriously impaired in adults) high concentrations of the drug are found which tend to increase with succeeding doses.

See section titled 'Gray Syndrome' under 'Adverse Reactions'.

Infants and Children with Immature Metabolic Processes

In young infants and other children in whom immature metabolic functions are suspected, a dose of 25 mg/kg/day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microbiological techniques where possible.

AVAILABILITY OF DOSAGE FORMS

Chloromycetin* Succinate is supplied in rubber diaphragm-capped vials containing chloramphenicol sodium succinate equivalent to 1 g chloramphenicol. The product has been freeze-dried in the vial. A dose of chloramphenicol sodium succinate equivalent to 1g of chloramphenicol contains approximately 52 mg (2.25 mEq) of sodium. Packages of 10.

Store at controlled room temperature (15^{o}-30^{o} C).

PHARMACEUTICAL INFORMATION

Drug Substance

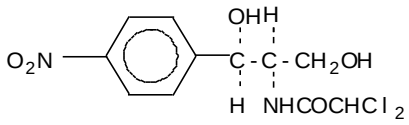
Proper Name: Chloramphenicol Sodium Succinate for Injection

Chemical Name: Sodium (2*R*,3*R*)-2-(2,2-dichloroacetamido)-3-hydroxy-3-(4-nitrophenyl)propyl succinate

Emperical Formula: $C_{15}H_{15}Cl_2N_2NaO_8$

Molecular Weight: 445.2

Structural Formula:



Chloramphenicol
Molecular Weight: 323.13