PRODUCT MONOGRAPH
Including Patient Medication Information

CHLOROMYCETIN* SUCCINATE INJECTION

(Chloramphenicol Sodium Succinate for Injection Ph.Eur)

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

Antibiotic

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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.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CHLOROMYCETIN SUCCINATE INJECTION and other antibacterial drugs, CHLOROMYCETIN SUCCINATE INJECTION should be used only to treat infections that are proven or strongly suspected to be caused by susceptible

bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

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.

Susceptibility/Resistance

Development of Drug Resistant Bacteria

Prescribing CHLOROMYCETIN SUCCINATE INJECTION in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

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

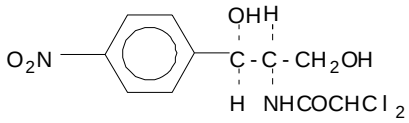
Proper Name: Chloramphenicol Sodium Succinate for Injection

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

Patient Medication Information

CHLOROMYCETIN* SUCCINATE INJECTION
Chloramphenicol Sodium Succinate for Injection Ph.Eur

Read this carefully before you start taking CHLOROMYCETIN* SUCCINATE INJECTION. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about CHLOROMYCETIN* SUCCINATE INJECTION .

What is CHLOROMYCETIN* SUCCINATE INJECTION used for?

CHLOROMYCETIN* SUCCINATE INJECTION is used to treat infections:

- caused by certain bacteria

Antibacterial drugs like CHLOROMYCETIN* SUCCINATE INJECTION treat only bacterial infections. They do not treat viral infections such as the common cold.

How does CHLOROMYCETIN* SUCCINATE INJECTION work?

CHLOROMYCETIN* SUCCINATE INJECTION is an antibiotic. It stops bacteria from growing.

What are the ingredients in CHLOROMYCETIN* SUCCINATE INJECTION?

Medicinal ingredients: chloramphenicol (as chloramphenicol sodium succinate).
Non-medicinal ingredients: none.

CHLOROMYCETIN* SUCCINATE INJECTION comes in the following dosage forms:

As a sterile powder for solution in a vial containing 1g chloramphenicol.

Do not use CHLOROMYCETIN* SUCCINATE INJECTION if you:

- are allergic to chloramphenicol .

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CHLOROMYCETIN* SUCCINATE INJECTION. Talk about any health conditions or problems you may have, including if you:

- have liver problems
- have kidney problems

- are pregnant
- are taking a medicine that may affect your bone marrow. If you are not sure if a medicine you take does this, talk to your doctor.

Other warnings you should know about:

Gray syndrome:

Gray baby syndrome is a toxic reaction that can happen in babies who are given CHLOROMYCETIN SUCCINATE INJECTION. This can be dangerous and can lead to death. Your doctor will be very careful when giving CHLOROMYCETIN SUCCINATE INJECTION to your baby. They will test your baby's blood during treatment. You should watch for the following symptoms in your baby: blue lips, grey colour of skin, irregular breathing, loss of appetite, low muscle tone, reduced muscle strength, swollen belly, vomiting. Get immediate medical help if you baby has any of these symptoms.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with CHLOROMYCETIN* SUCCINATE INJECTION:

- tolbutamide, a medicine used to treat diabetes
- phenytoin, a medicine used to treat seizures
- dicumarol, a medicine used to treat blood clots

How to take CHLOROMYCETIN* SUCCINATE INJECTION:

- CHLOROMYCETIN* SUCCINATE INJECTION will be given to you by a healthcare professional.
- It will be infused directly into your vein.
- You will receive it either 2, 3 or 4 times a day.
- Follow all instructions given to you by your healthcare professional.
- Although you may feel better early in treatment, CHLOROMYCETIN* SUCCINATE INJECTION should be used exactly as directed.
- Misuse or overuse of CHLOROMYCETIN* SUCCINATE INJECTION could lead to the growth of bacteria that will not be killed by CHLOROMYCETIN* SUCCINATE INJECTION (resistance). This means that CHLOROMYCETIN* SUCCINATE INJECTION may not work for you in the future.

Usual dose:

- Your healthcare professional will decide how much CHLOROMYCETIN* SUCCINATE INJECTION you will receive.

- Your healthcare professional will decide how often and for how long you will receive CHLOROMYCETIN* SUCCINATE INJECTION.

Overdose:

Overdosage can result in symptoms such as: nausea, vomiting and diarrhea.

If you think you have received too much CHLOROMYCETIN* SUCCINATE INJECTION , contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using CHLOROMYCETIN* SUCCINATE INJECTION?

These are not all the possible side effects you may feel when taking CHLOROMYCETIN* SUCCINATE INJECTION. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- nausea
- vomiting
- diarrhea

Your doctor will perform blood tests before you take CHLOROMYCETIN SUCCINATE INJECTION and while you are taking it.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Allergic reactions: difficulty breathing, difficulty swallowing, fever, hives, itching, rash, swelling of your tongue or throat.			✓
Headache		✓	
Mental health problems:		✓	

Confusion, depression, disorientation, inability to think clearly or pay attention, loss of touch with reality, reduced awareness.			
Sore mouth or tongue		✓	
RARE			
Anemia (decreased red blood cells): dizziness, fatigue, loss of energy, paleness, shortness of breath, weakness.		✓	
Enterocolitis (bowel inflammation): abdominal pain or tenderness, fever, severe diarrhea (bloody or watery), nausea, pain, mucus or pus in stool, vomiting.		✓	
Gray syndrome (toxic reaction that can happen in babies only and can lead to death): loss of appetite, vomiting, grey colour of the skin, blue lips , low body temperature, swollen belly, irregular breathing, low muscle tone, reduced muscle strength.			✓
Leukopenia (decreased white blood cells): aches, bleeding gums, feeling tired, fever, flu-like symptoms, infections, sore mouth and gums, mouth ulcer, rash.		✓	
Nerve damage: muscle weakness, numbness, prickling or tingling in your hand or feet, pain, sensitivity to touch.		✓	
Optic neuritis (inflammation of the eye): change in vision, flashing lights, pain, vision loss.		✓	
Thrombocytopenia (decreased platelets in the blood): bleeding, bruising, fatigue, weakness.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

• Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or

• Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store CHLOROMYCETIN* SUCCINATE INJECTION at room temperature (15 to 30°C).

- Keep out of reach and sight of children.

If you want more information about CHLOROMYCETIN* SUCCINATE INJECTION:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website (www.eci2012.net), or by calling 1-800-931-3133.

This leaflet was prepared by ERFA Canada 2012 Inc.

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