1 Chloramphenicol LINK 1g powder for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of Chloramphenicol LINK contains chloramphenicol sodium succinate equivalent to 1 g of chloramphenicol.

Chloramphenicol sodium succinate is a white or yellowish-white hygroscopic powder. It is soluble 1 in less than 1 part of water, 1 in 1 part of alcohol; practically insoluble in chloroform and ether. A 25% solution in water has a pH of 6.4 to 7.0.

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

MW: 445.2

Chemical Name: Chloramphenicol sodium succinate is a mixture of variable proportions of sodium (2R,3R)-2-(2,2-dichloroacetamido)-3-hydroxy-3-(4-nitrophenyl)-propyl succinate ('3-isomer') and sodium (1R,2R)-2-(2,2-dichloroacetamido)-3-hydroxy-1-(4-nitrophenyl) propyl succinate ('1-isomer').

There are no excipients in this product (see 6.1 List of excipients).

3 PHARMACEUTICAL FORM

Powder for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Chloramphenicol LINK is specifically indicated for bacterial meningitis, typhoid fever, rickettsial infections, intraocular infections and other serious infections where bacteriological evidence or clinical judgement indicates that chloramphenicol is an appropriate antibiotic.

4.2 Dose and method of administration

Chloramphenicol in the form of chloramphenicol sodium succinate may be administered intravenously or intramuscularly in seriously ill patients.

Dosage of 50 mg/kg/day administered in divided doses at six hourly intervals is recommended for the average patient. In exceptional cases, such as with patients having infections due to moderately resistant organisms or suffering from infections such as septicaemia or meningitis, dosage schedules up to 100 mg/kg/day may be prescribed. However, these high doses should be decreased as soon as clinically indicated.

In instances of impaired hepatic or renal function, the ability to metabolise or excrete chloramphenicol may be reduced and the medical practitioner should adjust the dose accordingly.

Premature and Newborn Infants and Children with Immature Metabolic Processes

Refer to grey baby syndrome under 4.8 Undesirable effects, Cardiac Disorders. A total of 25 mg/kg/day divided into four doses at six hour intervals usually produces and maintains a concentration of chloramphenicol in blood and tissues adequate to control most infections in premature and newborn infants and children with immature metabolic processes.

After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg/kg/day divided equally into four doses at six hour intervals. Precise control of serum blood levels, when in doubt, may be achieved through analytical methods.

Preparation For Use

This product contains no additional antimicrobial agent. It is for single use in one patient only. Discard any residue.

The powder in the vial is prepared for injection by the addition of an aqueous diluent such as water for injections, 0.9% sodium chloride injection or 5% glucose injection. Although Chloramphenicol LINK freeze dried powder is highly soluble, with the lower concentrated solutions taking approximately 2 minutes, the rate of solution is somewhat slower in the more highly concentrated solutions. Gentle shaking of the vial hastens solution or solubility, however the more highly concentrated solutions may take more than 10 minutes. The following dilution table may be used as a guide for preparing solutions for injections.

Preparation of Chloramphenicol LINK Solution for Injection Dilution Table

%	Strength of solution	**Add diluent**	Displacement value	Total volume after dilution
40	400 mg/mL	**1.7 mL**	0.8 mL/1 g (vial)	2.5 mL
25	250 mg/mL	**3.2 mL**	0.8 mL/1 g (vial)	4.0 mL
10	100 mg/mL	**9.2 mL**	0.8 mL/1 g (vial)	10.0 mL

Susceptibility Tests

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "susceptible" indicates the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "intermediate" indicates that the result should be considered equivocal and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in the body sites where the drug is physiologically concentrated or in situations where high dosage of the drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of "resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

4.3 Contraindications

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reactions to the product or its components.

4.4 Special warnings and precautions for use

Chloramphenicol is a potent therapeutic agent and should not be used for trivial infections or for prophylaxis. The use of chloramphenicol sodium succinate injection should be reserved for serious infections when other less hazardous antimicrobial agents are ineffective or contraindicated.

Chloramphenicol must be administered according to the instructions of a medical practitioner.

Use in Hepatic and Renal Impairment

Reduced doses should be given to patients with hepatic impairment. Excessive blood concentrations may also occur following administration of usual doses to patients with severe renal impairment and in premature and full-term neonates who have immature metabolic processes. Monitoring of plasma chloramphenicol concentrations may be desirable in patients with risk factors. A suggested range for peak plasma concentrations is 10 to 25 µg/mL and for trough concentrations 5 to 15 µg /mL.

Use in Premature and Full-Term Neonates

Due to the risk of "grey baby syndrome" (see 4.8 Undesirable effects), neonates should not be given chloramphenicol systemically, unless it is potentially life saving and there is no alternative.

Use During Immunisation

Chloramphenicol may interfere with the development of immunity and should not be used during active immunisation.

Use in Pre-Existing Haematological Disorders

Use with caution in patients with pre-existing haematological disorders or in patients who are receiving other bone marrow depressants.

Blood dyscrasias including aplastic anaemia are known to occur after administration of chloramphenicol. If facilities are available, it is well to determine the routine blood profile before therapy, and blood studies should be repeated at appropriate intervals especially during prolonged or intermittent therapy. Consideration should be given to discontinuing the drug if evidence of depression of any of the blood elements appears attributable to chloramphenicol, weighing these effects against the seriousness and course of the disease under treatment. Repeated courses of chloramphenicol and concurrent therapy with other drugs known to cause bone marrow depression or aplastic anaemia should be avoided.

There have been reports of aplastic anaemia attributed to chloramphenicol which later terminated in leukaemia (see 4.8 Undesirable effects). Treatment should not be continued longer than to produce a cure with little or no risk of relapse. Aplastic anaemia usually occurs after treatment has been completed. Patients should be informed of the importance of having blood counts followed closely during therapy.

Prolonged Use

Prolonged use of chloramphenicol may induce bleeding, either by bone-marrow depression or by reducing intestinal flora with consequent inhibition of vitamin K synthesis. Prolonged use may also cause haemolytic episodes in individuals with glucose 6-phosphate dehydrogenase (G-6-PD) deficiency.

Optic and peripheral neuritis have been reported usually following long term dosage (see 4.8 Undesirable effects).

Pseudomembranous Colitis

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including chloramphenicol. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable

oral antibacterial agent effective against *C. difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs that delay peristalsis, e.g. opiates and diphenoxylate with atropine (LOMOTIL®) may prolong and/or worsen the condition and should not be used.

As with other antibiotics, the use of chloramphenicol may result in an overgrowth of non-susceptible organisms including fungi. If infections caused by non-susceptible organisms occur during therapy, appropriate measures should be taken.

4.5 Interaction with other medicines and other forms of interaction

In those patients who are concurrently receiving anticoagulants or anticonvulsants, dosage adjustment of these agents may be necessary. 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.

Alfentanil - chronic preoperative or perioperative use of chloramphenicol, may decrease the plasma clearance and prolong the duration of action of alfentanil.

Oral contraceptives containing oestrogen - concurrent long term use of chloramphenicol may result in reduced contraceptive reliability and increased incidence of breakthrough bleeding.

Hepatic Enzyme Induction - concurrent use of chloramphenicol with hepatic microsomal enzyme inducing drugs, including phenobarbitone and rifampicin, can increase the metabolism of chloramphenicol, decreasing chloramphenicol serum concentrations.

Hepatic Enzyme Inhibition - inhibition of the cytochrome P-450 system by chloramphenicol may cause a decrease in the hepatic metabolism of other medications metabolised by the mixed-function oxidase system, resulting in delayed elimination and increased blood concentrations.

Tacrolimus - chloramphenicol has been shown to increase the 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 Fertility, pregnancy and lactation

Use in Pregnancy: Category A

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

Chloramphenicol enters the foetal circulation and, if given to the mother shortly before parturition, may cause "grey baby syndrome", with cyanosis and hypothermia, owing to the limited glucuronidating capacity of the newborn infant's liver. It may also cause bone marrow suppression in the neonate. Chloramphenicol treatment should therefore be avoided during the week before parturition.

Use in Lactation

Due to the possibility of toxic effects on the nursing infant (see 4.6 Fertility, pregnancy and lactation), the use of chloramphenicol is not recommended during breastfeeding.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Blood and Lymphatic System Disorders: Blood dyscrasias including aplastic anaemia, hypoplastic anaemia, thrombocytopenia and granulocytopenia have been attributed to the administration of chloramphenicol (see 4.4 Special warnings and precautions for use). A reversible type of bone marrow depression, which is dose-related, may occur. This type of marrow depression is characterised by vacuolisation of the erythroid cells, reduction of reticulocytes and leucopenia, and responds promptly to the withdrawal of chloramphenicol. An irreversible type of marrow suppression leading to aplastic anaemia, with a high mortality rate, is characterised by the appearance of bone marrow aplasia or hypoplasia weeks or months after therapy. The incidence of fatal aplastic anaemia has been estimated as 1 in 40,000 to 1 in 100,000 based on two dosage levels. Peripherally, pancytopenia is observed most often, but in a small number of cases only one or two of the three major cell types (erythrocytes, leucocytes, platelets) may be depressed. Paroxysmal nocturnal haemoglobinuria has also been reported.

Gastrointestinal Disorders: Nausea, vomiting, glossitis and stomatitis, diarrhoea and enterocolitis may occur; incidence is low.

Nervous System Disorders: Headache; peripheral neuritis has been reported usually following long-term dosage. If this occurs, the drug should be promptly withdrawn.

Psychiatric Disorders: Mild depression, mental confusion and delirium.

Eye Disorders: Optic neuritis has been reported usually following long-term dosage. If this occurs, the drug should be promptly withdrawn.

Immune System Disorders: Anaphylaxis; Herxheimer reactions have occurred during therapy for typhoid fever.

Skin and Subcutaneous Tissue Disorders: Angioedema, macular and vesicular rashes, urticaria.

Cardiac Disorders: Toxic reactions including fatalities have occurred in premature and newborn infants; the signs and symptoms associated with these reactions are known as the grey baby syndrome. Although "grey baby syndrome" has been reported in neonates born to mothers that have received chloramphenicol during labour, in most cases therapy with chloramphenicol has been instituted within the first 48 hours of life and symptoms first appeared after 3 to 4 days of continued treatment with high doses of chloramphenicol. Single reports have appeared in infants as old as three months.

The manifestations in the first 24 hours are vomiting, refusal to suck, irregular and rapid respiration, abdominal distension, periods of cyanosis and passage of loose green stools. After 24 hours, the infant develops flaccidity, an ashen grey colour, a decrease in temperature, followed by circulatory collapse.

Mechanisms responsible for this effect are the inadequate development of hepatic and renal function.

General Disorders and Administration Site Conditions: Fever

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Levels exceeding 25 µg/mL are frequently considered toxic. Chloramphenicol toxicity can be evidenced by serious haemopoietic effects such as aplastic anaemia, thrombocytopenia, leukopenia, as well as increasing serum iron levels, nausea, vomiting and diarrhoea. In the case of serious overdosage, charcoal haemoperfusion may be effective in removing chloramphenicol from plasma. Exchange transfusion is of questionable value following massive overdosage, especially in neonates and infants.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Chloramphenicol sodium succinate is a prodrug. After parenteral administration it is hydrolysed in the liver to produce free active chloramphenicol. The rate of hydrolysis is variable in different individuals.

Chloramphenicol is effective in a wide variety of bacterial and rickettsial infections. It possesses high antimicrobial activity, crosses tissue barriers readily, and diffuses widely and rapidly through nearly all body tissues and fluids.

5.2 Pharmacokinetic properties

Inter-individual variation exists in determining the pharmacokinetics for a given patient with impaired and/or immature hepatic or renal function (see 4.2 Dose and method of administration).

Intramuscular chloramphenicol sodium succinate may produce lower blood concentrations than identical intravenous doses. Intramuscular absorption is slow and produces peak blood levels in approximately 2 to 4 hours.

Distribution

Chloramphenicol has high lipid solubility and diffuses rapidly throughout tissues and body fluids, with highest concentrations in the liver and kidneys. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation. Measurable levels are also detectable in pleural and ascitic fluids, saliva and in milk. It diffuses readily into the aqueous and vitreous humours of the eye. Transport across the placental barrier occurs with somewhat lower concentration in cord blood than in maternal blood.

Metabolism and Excretion

Following intravenous or intramuscular administration, chloramphenicol sodium succinate must be hydrolysed to free chloramphenicol within the body. Part of the parenterally administered chloramphenicol sodium succinate is excreted by the kidneys prior to hydrolysis. Although serum levels of free chloramphenicol are lower than when a comparable dose of chloramphenicol is given orally, they are clinically effective.

In adults, approximately 90% of chloramphenicol is metabolised primarily in the liver by glucuronyl transferase and excreted in the urine. Total urinary excretion ranges from 68% to over 90%, and 30% is excreted as unchanged chloramphenicol. Metabolism and elimination vary widely among patients.

The elimination half-life has been estimated to be in the range 1.6 to 3.3 hours, but is variable in patients with hepatic impairment and prolonged (to 28 hours) in neonates.

5.3 Preclinical safety data

Microbiology

In vitro chloramphenicol exerts mainly a bacteriostatic effect on a wide range of Gram-negative and Gram-positive bacteria and is also active against rickettsial organisms and the lymphogranuloma-psittacosis group and Vibrio cholerae. It is particularly active against Salmonella typhi and Haemophilus influenzae. The mode of action is through interference with, or inhibition of, protein synthesis in intact cells and cell-free systems. Antagonism has been demonstrated in vitro between chloramphenicol, erythromycin, clindamycin and lincomycin. Development of resistance to chloramphenicol, both experimentally and in man, appears to be low in contrast to other antibiotics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

There are no excipients in this product.

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

Cloudy solutions of Chloramphenicol LINK should not be used. To reduce microbiological hazard, use as soon as practicable after reconstitution. If storage is necessary, hold at 2°C to 8°C for not more than 24 hours.

6.5 Nature and contents of container

Chloramphenicol LINK is supplied in a clear glass vial sealed with a rubber stopper and aluminium cap or flip-off cap, containing 1 g of chloramphenicol, as chloramphenicol sodium succinate freeze dried powder: Supplied in packs of 1 vial (solvent required).

6.6 Special precautions for disposal <and other handling>

No special requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

31 December 1969

10 DATE OF REVISION OF THE TEXT

26 July 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformat of data sheet to new requirement.
4.2	Addition of solution preparation times.