Package leaflet: Information for the patient

Chloramphenicol 1 g Powder for Injection
(referred to as "Chloramphenicol Injection" throughout the text)

chloramphenicol
Powder for solution for injection

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Chloramphenicol Injection is and what is it used for

This medicine contains chloramphenicol sodium succinate, which is an antibiotic used to treat severe infections such as typhoid and meningitis and should only be used when other antibiotics do not help or are unsuitable. It is also used when oral chloramphenicol cannot be used or when higher amounts of the medicine is needed in the blood.

Chloramphenicol prevents bacteria making an essential nutrient required for growth and multiplication. In time, the number of bacteria are reduced and the infection is controlled, so that treatment can be continued using a more gentle antibiotic.

You must talk to a doctor if you do not feel better or if you feel worse.

2. What you need to know before you are given Chloramphenicol Injection

Do not use Chloramphenicol Injection:
- If you have had an allergic reaction (e.g. rash, wheezing) to chloramphenicol before.
- If you are pregnant, or are breast-feeding.

Warnings and precautions:
Talk to your doctor or pharmacist:
- If you have a history of kidney or liver disease.
- If you are already taking any other medicines which may also cause bone marrow depression.

- If you have a cold, viral influenza, throat infection and before using this medicine to prevent bacterial infections.
- If you have recently been or are about to be vaccinated.

This medicine is associated with various forms of anaemia (a decrease in red blood cells, white blood cells and platelets), which in turn leads to a loss of immunity and can progress into leukaemia. It should only be prescribed if less toxic antibiotics are not available.

New born babies should be treated with care to avoid Grey Syndrome, which is a serious condition arising from excessive toxic chloramphenicol metabolites. Treatment should be terminated as soon as symptoms are identified.

There is a risk of over-growth of non-susceptible organisms, which can lead to severe diarrhoea up to a few months after this medicine is given to the patient.

Other medicines and Chloramphenicol Injection:
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

The following medicines interact with Chloramphenicol Injection, which affects the way that one or the other medicine works:

- anticoagulants of the coumarin-type (to thin your blood or stop it clotting), antidiabetic agents (e.g. tolbutamide), anti-epileptic agents (e.g. phenytoin and phenobarbital) or rifampicin (an antibiotic).

Pregnancy and breast-feeding
Do not use Chloramphenicol Injection if you are pregnant, or are breast-feeding.

Driving and using machines
No effect on the ability to drive or use machinery is expected with Chloramphenicol Injection.

Chloramphenicol Injection contains sodium
This medicine contains 71.2 mg sodium in each vial. This is equivalent to 3.6% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Chloramphenicol Injection is given to you

Chloramphenicol Injection will be made into a solution and be given to you by injection into a vein, or into a muscle under the direction of a medical practitioner. Your doctor will prescribe the required amount (the dose). The dose is decided by taking into account the severity of your condition.

Adults:
The recommended dosage for adults is; 1 g of chloramphenicol every 6-8 hours.

Use in children and adolescents:
The recommended dose for children is; 50 mg/kg of chloramphenicol daily in divided doses every 6 hours (no more than this should be given); and 25 mg/kg daily in divided equal doses every 6 hours in new-born and premature infants.

The doctor may give you more in certain cases e.g. if you have septicaemia or meningitis (100 mg/kg/day), but should then be decreased as soon as appropriate. Your doctor will decide how long you need to be treated for.

During treatment your doctor will carry out blood tests to check that:

- Your blood is functioning properly as Chloramphenicol Injection can damage your blood cells.
- Your liver and kidneys are functioning properly as Chloramphenicol Injection may affect these organs.

If you are given more Chloramphenicol Injection than you should
In the case of serious overdosage, charcoal haemoperfusion may be effective in removing chloramphenicol from your blood.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor **immediately** if any of the following side effects occur:

- Severe allergic reaction e.g. red raised areas on your skin which may look like spots or be several inches across, which cause itchiness.
- Grey Syndrome – usually in new-born or premature infants, where the skin appears grey, and the infant is listless and weak.
- White blood cell counts (which fight infection) can also drop, increasing the chance of infections, bruising and fever.
- Anaemia (a low red blood cell count) that can leave you feeling tired and lethargic.

Other side effects may occur, but, the frequency cannot be estimated from the available data:

- Dry mouth.
- Nausea (feeling sick), vomiting (being sick) and diarrhoea.
- Headache.
- Depression.
- Inflammation or damage to the nerves causing numbness, tingling, pain or muscle weakness.
- Blurring, inflammation or temporary loss of vision.
- Chloramphenicol may slow down development of immunity, and you may develop infections more frequently, which are difficult to fight off.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet.
You can also report side effects directly via the Yellow Card Scheme at:
www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Chloramphenicol Injection

Do not use this medicine after the expiry date which is stated on the vial label and on the carton after EXP. The expiry date refers to the last day of that month.

Keep container in the outer carton. Keep this medicine out of the sight and reach of children.

6. Contents of the pack and other information

What Chloramphenicol Injection contains:

The active substance is chloramphenicol sodium succinate. There are no other ingredients found in Chloramphenicol Injection.
(See end of Section 2 for further information on sodium).
What Chloramphenicol Injection looks like and contents of the pack

Chloramphenicol Injection is available as single glass vials. Each vial contains a freeze-dried powder containing the equivalent of 1 g chloramphenicol.

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Healthcare Professional Information Leaflet

Chloramphenicol 1 g Powder for Injection
Chloramphenicol sodium succinate equivalent to 1 g chloramphenicol.
Powder for solution for injection

After parenteral administration chloramphenicol is rapidly released from chloramphenicol sodium succinate. Chloramphenicol Injection (chloramphenicol) is a broad spectrum antibiotic and is active against many gram-positive organisms and gram-negative organisms, spirillae and rickettsia. It acts by interfering with bacterial protein synthesis. Chloramphenicol is widely distributed in body tissues and fluids and enters the cerebrospinal fluid. Chloramphenicol sodium succinate, free chloramphenicol and metabolites are excreted in the urine.

After intravenous administration of chloramphenicol succinate every 6 hours elimination half lives were 4.03 hours for chloramphenicol and 2.65 hours for chloramphenicol succinate. After

intravenous chloramphenicol sodium succinate, steady state peak concentrations were reached on average 18.0 minutes after cessation of the infusion. In infants and children aged 3 days to 16 years the apparent half-life was extremely variable ranging from 1.7 to 12.0 hours.

Indications
Chloramphenicol Injection should not be used for trivial infections due to the possibility of severe blood dyscrasias which may prove fatal. Chloramphenicol Injection is indicated for typhoid, meningitis caused by *H. influenzae* and other serious infections caused by bacteria susceptible to chloramphenicol. It is also indicated wherever chloramphenicol is deemed the antibiotic of choice and oral administration is not possible, or where higher than usual blood concentrations are required.

Dosage and administration
Posology
The dose administered and the concentration used is dependent on the severity of the infection.

Recommended standard dosage

***Adults*:** The equivalent of 1 g of chloramphenicol every 6-8 hours.

Elderly: The usual adult dosage should be given subject to normal hepatic and renal function.

Children: The equivalent of 50 mg/kg chloramphenicol, according to body weight, daily in divided doses every 6 hours (this dose should not be exceeded). The patient should be carefully observed for signs of toxicity.

Premature Infants and Neonates: 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.

Dosage in special clinical conditions In exceptional cases, such as patients with septicaemia or meningitis, dosage schedule up to 100 mg/kg/day may be prescribed. However, these high doses should be decreased as soon as clinically indicated. To prevent relapses, treatment should be continued after the temperature has returned to normal for 4 days in rickettsial diseases and for 8-10 days in typhoid fever.

Method of administration
To be given by intravenous injection or infusion or by intramuscular injection. In order to ensure rapid attainment of high blood levels, Chloramphenicol Injection is best administered intravenously. Where this is not possible, intramuscular administration may be used, although absorption may be slow and unpredictable. The use of the intramuscular route should be restricted to those patients where parenteral administration is considered most appropriate but intravenous use is impossible or impractical.

Intravenous administration should be as a 10% (100 mg/mL) solution to be injected over at least a one-minute interval, or in a larger volume of fluid, by slow intravenous infusion after reconstitution. The same 10% (100 mg/mL) solution can also be administered intra-muscularly, if necessary.

Since the recommended dose for neonates and premature infants is 25 mg/kg daily, divided in multiple doses, it might be difficult to achieve such a dose with 100 mg/ml (10%) concentration in case of a small infant. In such cases, a solution of lower concentration may be used.

Chloramphenicol Injection should be administered intravenously as a 10% (100 mg/ml) solution or lower, that can be prepared by diluting the lyophilized powder in the vial with 9.2 ml of diluent (see table below).

The resulting solution can be administered as an intravenous bolus, intravenous infusion or intramuscular injection. The use of the intramuscular route should be, however, restricted only to those patients where intravenous access is unavailable.

The solution can be reconstituted with the following diluents:

- Water for injections
- 0.9% sodium chloride
- 5% dextrose

1 vial containing 1.377 g of chloramphenicol sodium succinate (equivalent to 1.0g of laevorotatory chloramphenicol	Route of administration	Amount of diluent to be added (ml)	Resulting concentration in mg/ml (%)
	Intravenous bolus (1 minute) Slow intravenous infusion Intramuscular injection	9.2 ml	100 mg/ml (10%)

**Includes 0.8 ml water from gaseous phase in vial*

The colour of solution following re-constitution is a clear-yellowish solution.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Contraindications and warnings

Chloramphenicol Injection is contraindicated in patients with a previous history of sensitivity and/or toxic reactions to chloramphenicol. It is also contraindicated in pregnancy and whilst breast feeding. Chloramphenicol Injection is to be administered only under the direction of a medical practitioner. It should be reserved for serious infections caused by organisms susceptible to its antimicrobial effects when less toxic antibiotics are ineffective or contraindicated. However, chloramphenicol may be chosen to initiate antibiotic therapy based on the clinical impression. *In vitro* sensitivity tests should be performed concurrently so that the drug may be discontinued as soon as possible if a less toxic antibiotic is 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.

<u>Bone marrow depression and blood disorders</u>

Serious and fatal blood dyscrasias (aplastic anaemia, hypoplastic anaemia, thrombocytopenia, granulocytopenia, and bone marrow depression) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anaemia attributed to chloramphenicol, which later resulted in leukaemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used in the treatment of any infection for which a less toxic antibiotic is available.

Patient monitoring

Because of its toxic nature it is important to monitor serum levels of this antibiotic particularly in new-born and premature infants, in the elderly, in patients with renal or hepatic disease and in those receiving other drugs with which chloramphenicol may interact.

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

It is desirable that patients be hospitalised during therapy, so that appropriate laboratory determinations and clinical observations can be made.
Baseline haematologic determinations should be made and determinations repeated approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leucopoenia, thrombocytopenia, anaemia, or any other haematologic 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.

The following may become apparent after chloramphenicol treatment: dryness of the mouth, nausea and vomiting, diarrhoea, urticaria, optic neuritis with blurring or temporary loss of vision, peripheral neuritis, headache and depression. Chloramphenicol has been shown to interact with, and enhance the effects of coumarin anticoagulants, some hypoglycaemic agents (e.g. tolbutamide) and phenytoin. When given concurrently, a dose reduction of these agents may, therefore, be necessary. Plasma concentration of chloramphenicol may be reduced with concomitant usage of phenobarbital and rifampicin. Chloramphenicol may impede the development of immunity and should therefore not be given during active immunisation.

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.

Grey syndrome in infants and neonates

Precaution should be used in therapy of premature and full-term neonates to avoid "Grey 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 "Grey Syndrome". Although "Grey Syndrome" has been reported in neonates born to mothers after having received

chloramphenicol during labour, in most cases therapy with chloramphenicol has been instituted within the first 48 hours of life. The following summarises 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.

Superinfections
The use of chloramphenicol, as with other antibiotics, may result in an overgrowth of non-susceptible organisms, including fungi. If infections caused by non-susceptible organisms appear during therapy, appropriate measures should be taken.
Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including chloramphenicol, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*
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 diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Pharmaceutical precautions
Keep container in the outer carton.

Package quantities
Individual vials containing chloramphenicol sodium succinate equivalent to 1 g chloramphenicol.

POM

PL 41871/0015

Keep all medicines out of the sight and reach of children.

Manufactured by:
Delpharm Saint Remy
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