SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Chloramphenicol Fisiopharma 1 g

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial with powder contains:
Active substance: chloramphenicol sodium succinate 1.378 g (equivalent to chloramphenicol 1 g).

3. PHARMACEUTICAL FORM
Powder for solution for injection for intravenous use.
White or yellowish-white powder.

4. CLINICAL PARTICULARS
4.1 Therapeutic indication
Chloramphenicol is active against several bacteria in the following infections:
- Typhoid fever and salmonellosis *(Salmonella typhi)*;
- Bacterial meningitis *(Haemophilus influenzae, Neisseria meningitidis)*;
- Rickettiosis *(Rickettsia)*;
- Brucellosis *(Brucella)*;
- Psittacosis *(Chlamydophila psittaci)*;
- Lymphogranuloma Venereum *(Lymphogranuloma-psittacosis)*;
- Urinary infection caused by gram-negative bacteria;
- Infections caused by anaerobic bacteria *(Cocci gram-positive cocci, Clostridium)*.

and is indicated when oral administration is contraindicated or not feasible due to vomiting, diarrhea or severe sepsis.

4.2 Posology and method of administration
The product should be administered via the intravenous route.
Recommended dosages:

Adults and adolescents
The recommended dose for the treatment of most infections is 50-100 mg/kg/day divided into 4 daily administrations (1 administration every 6 hours).

Infants up to 2 weeks
The recommended dose for the treatment of most infections is 25 mg/kg/day divided into 4 daily administrations (1 administration every 6 hours).
For infants under 1 week or weighing less than 2 kg the recommended dose is 25 mg/kg/day every 24 hours (1 administration daily).
For infants over 1 week and weighing more than 2 kg, the recommended dose is 25 mg/kg/day devided into 2 daily administrations (1 administration every 12 hours).

Infants over 2 weeks and children (up to 12 years)
The recommended dose for the treatment of most infections is 50 mg/kg/day divided into 4 daily administrations (1 administration every 6 hours).

Impaired renal function
Although chloramphenicol does not accumulate significantly even in the presence of reduced renal function, patients with this condition may find more difficult to eliminate the drug and may need a dosage adjustment. To determine if a dosage adjustment is necessary, blood levels of the drug should be monitored frequently.

Impaired hepatic function
Patients with a reduced liver function may have a reduced ability to eliminate the drug and, therefore, dosage adjustment may be necessary. To determine if a dosage adjustment is necessary, blood levels of the drug should be monitored.
For patients with hepatic impairment it is recommended to use a loading dose of 1 g followed by 500 mg every 6 hours.
For patients with liver cirrhosis the recommended dose is 500 mg every 6 hours.
For patients suffering from jaundice, the dose of 25 mg/kg/day should not be exceeded.

Dialysis patients
The amount of drug removed from haemodialysis is not such as to justify a dosage adjustment in all the cases.
There is no need to change the dosage in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) or continuous arterio-venous hemofiltration (CAVH).
The injectable solution must be prepared extemporaneously by dissolving the powder in water for injectable preparations, saline solution or 5% glucose solution, at the desired concentrations.

4.3 Contraindications
- Hypersensitivity to the active substanceor to any of the excipients;
- Bone marrow depression;
- Breastfeeding.

Chloramphenicol should not be administered for the treatment of minor infections or for prophylaxis.
Chloramphenicol may interfere with immunity mechanisms and should not be administered during the active immunisation phase (see section 4.5).

4.4 Special warnings and precautions for use
Limit the administration of the antibiotic strictly to the period indicated by the specific recommendations for each infection, possibly no later than 2 weeks. During the treatment with chloramphenicol it is necessary to carefully monitor the haematological parameters.
In fact, the administration of chloramphenicol, in high doses and for prolonged and repeated therapies, can induce the onset of aplastic anaemia, detectable even weeks or months after discontinuation of treatment.
In patients with impaired blood flow, chloramphenicol should be used with great caution. In prolonged or repeated therapies, blood pressure must be monitored frequently, stopping treatment immediately if leukocytes decrease below 4000 per mm^3 and granulocytes of 40% (unless they are leukopenising infections in themselves such as typhoid fever); late complications may occur.
The use of chloramphenicol may also result in a decrease in prothrombin time for inhibition of the intestinal bacterial flora that produces vitamin K.
In patients suffering from hepatic or renal failure, dose adjustment may be necessary (see section 4.2 Posology and method of administration).
Treatment with chloramphenicol, as with other antibiotics, may result in superinfections with insensitive bacterial agents or fungi.

4.5 Interaction with other medicinal products and other forms of interaction
Chloramphenicol is an inhibitor of cytochrome P450 and, therefore, may result in an increase in the half-life of several drugs with consequent increase in their toxicity. Chloramphenicol decreases the metabolism of the following drugs:
- dicoumarol and warfarin;
- phenytoin and phosphenytoin;
- clopidogrel;
- voriconazole;
- cyclophosphamide;
- ciclosporin;
- tacrolimus;
- phenobarbital;
- rifampicin.

Chloramphenicol may also interact with the following drugs:
- paracetamol: may cause an increase in the toxicity of chloramphenicol;
- beta-lactam antibiotics (penicillins and cephalosporins): antagonism with chloramphenicol may occur;
- cyanocobalamin: chloramphenicol may decrease the effect of cyanocobalamin;
- entacapone: chloramphenicol may cause a reduction in the biliary excretion of entacapone with a consequent increase in toxicity;
- hypoglycaemic sulphonamides (tolbutamide, chlorpropamide, glimepiride, etc.): chloramphenicol can cause an excessive hypoglycaemic response;
- iron: chloramphenicol decreases the effectiveness of iron;
- methotrexate: chloramphenicol, by inhibiting the intestinal bacterial flora, decreases intestinal absorption of methotrexate.

Furthermore, chloramphenicol may interfere with immunity mechanisms and should not be administered during the active immunisation phase, for example with tetanus toxoid or live typhoid vaccine.
Chloramphenicol may result in a false positive result in the test that exploits the copper reduction method for the determination of glucose in urine. In patients treated with chloramphenicol, urine tests based on glucose oxidase reactions should be used.

4.6 Pregnancy and breastfeeding

Pregnancy
Data on a large number of exposed pregnancies do not indicate particular side effects of chloramphenicol on pregnancy and on the health of the foetus/newborn, with the exception of the late stages of pregnancy, during which "gray baby syndrome", sometimes even lethal, may occur (fatal (see section 4.8). Therefore, chloramphenicol should not be used during the pregnancy unless clearly necessary.

Breastfeeding
Chloramphenicol is excreted in human milk. Although chloramphenicol concentrations are probably too low to induce "gray baby syndrome" (see section 4.8), this risk cannot be completely excluded. Furthermore, the bone marrow depression or other serious adverse effects to the infant may occur. Therefore, chloramphenicol should not be used during the breastfeeding period.

4.7 Effects on the ability to drive and use machines
Chloramphenicol Fisiopharma does not alter the ability to drive and use machines.

4.8 Undesirable effects
Below, the undesirable effects of chloramphenicol organized according to the MedDRA organic system classification are described. There are insufficient data to establish the frequency of the single listed effects.

Blood and lymphatic system disorders
Bone marrow depression: it can occur in two different forms: the first, dose-dependent characterised by agranulocytosis, anaemia, leukopenia, thrombocytopenia and reticulocytopenia; the second, not-dose-related, is a very severe form of aplastic anaemia which develops after a latency period of weeks or even months.

Depression of erythropoiesis is more frequent in patients with hepatic or kidney failure.

Trauma, poisoning and procedure complications.
"Grey baby syndrome": this toxic manifestation is observed in new-borns who are given high doses of chloramphenicol. It is characterised by abdominal distension, vomiting, ash colour, hypothermia, progressive cyanosis, circulatory collapse and death within a few hours or days. It appears that the cause may be the lack of glucuronoconjugation of chloramphenicol, due to inadequate hepatic glucuronyltransferase activity during the first weeks of the neonatal life, and inadequate renal excretion of the unconjugated drug.

Gastrointestinal disorders
Nausea, vomiting, unpleasant taste sensation (dysgeusia), diarrhoea, stomatitis, glossitis, enterocolitis, perineal irritation.

Immune system disorders
Hypersensitivity reactions with the onset of fever, rashes, anaphylaxis.

Nervous system disorders
Optical or peripheral neuritis, ototoxicity, headache, mental confusion.

Infections and infestations
Jarisch-Herxheimer reaction, characterised by shivers, headache, fever and mucocutaneous lesions.

Psychiatric disorders
Mild depression and delirium.

Respiratory, thoracic and mediastinal disorders
Bronchospasm

Hepatobiliary disorders
Hepatotoxicity

Reporting of adverse reactions
Reporting of suspected adverse reactions after the authorization of the medicinal product is important, as it allows continuous monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose
An overdose increases the risk of mainly haematological complications related to the direct toxicity of chloramphenicol (see section 4.8 Undesirable effects).
Chloramphenicol is only partially removed from the blood through peritoneal dialysis or haemodialysis. Both complete blood transfusions and charcoal haemoperfusion for chloramphenicol overdoses were used in newborns.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antibacterials for systemic use, carbapenems, ATC code: J01BA01.

Chloramphenicol is a broad-spectrum antibiotic with a bacteriostatic action. Usually bacteriostatic, chloramphenicol can be bactericidal at very high concentrations or against very sensitive microorganisms. Chloramphenicol inhibits the protein synthesis of bacteria and to a lesser extent that of eukaryotic cells. It acts by reversibly binding to the 50S subunit of the bacterial ribosome, thereby inhibiting protein synthesis.
Generally susceptible microbial species (mic ≤ 5 µg/ml) are: Streptococci (groups A and B), Streptococcus pneumoniae (Pneumococcus), Neisseria gonorrhoeae (Gonococcus), Neisseria meningitis (Meningococcus); Bacillus subtilis, Corynebacterium, Listeria; Salmonella, Shigella, Brucella, Pasteurella, Haemophilus, Compybacter, Vibrio; Anaerobes (Bacterioides, Clostridium, Fusobacterium, Aeromonas); Rickettsie, Mycoplasma, Chlamydiae.
The microbial species which are not always sensitive: Staphylococci, Enterococci, Colibacilli, Klebsiella, Proteus.
The following species are resistant (mic ≥ 25 µg/ml): Serratia, Acinetobacter, Pseudomonas.
The main mechanism of bacterial chemoresistance to chloramphenicol for gram-negative species consists of the enzymatic acetylation of the molecule, mediated by a factor R. This resistance has the characteristic of intra- and interspecies transferability. Resistance to chloramphenicol is also plasmid-mediated for gram-positive bacteria. A single plasmid can confer resistance to several antibiotics; for example, in the case of salmonella, resistance extends to tetracyclines, streptomycin and sulfonamides. You may have cross-resistance to thiamphenicol. Pseudomonas aeruginosa and certain strains of Proteus and Klebsiella resist chloramphenicol by a non-enzymatic mechanism comprising an inducible block of permeability.

5.2 Pharmacokinetic properties

Absorption
Chloramphenicol sodium succinate, administered parenterally, is hydrolysed in the liver, lungs and kidneys. Hydrolysis of chloramphenicol succinate is only partial, so the blood concentration of chloramphenicol after parenteral administration is lower than that obtained after oral administration.

Distribution
Chloramphenicol spreads rapidly, but its distribution is not uniform. The highest concentrations are in the liver and kidney; the lowest concentrations are in the brain and cerebrospinal fluid. Chloramphenicol penetrates into the cerebrospinal fluid even in the absence of inflammatory state of the meninge and reaches concentrations equal to about half those of blood. Measurable levels are also found in pleural and ascitic fluids, saliva, milk, and aqueous and vitreous humours. In addition, chloramphenicol crosses the placental barrier.

The volume of distribution is about 0.5 l/kg.
50%-80% of the dose is bound to plasma proteins.

Metabolism
Chloramphenicol is rapidly metabolised at the hepatic level especially in derivatives with glucuronic acid, microbiologically inactive, which are rapidly excreted by the kidney. It should be necessary to consider that in newborns the capacity for glucuronidation and renal elimination is very limited.

Elimination
Chloramphenicol is excreted mainly through the kidney (90%) as a glucuronic acid conjugate and, to a small extent, also in unchanged form. Small amounts are excreted in bile (2-3%) and faeces (1%).
The plasma half-life varies between 1.5 and 5 hours.
In patients suffering from renal failure, the half-life varies from 3 to 7 hours.
In patients suffering from reduced renal function, the half-life is generally prolonged, especially in patients with cirrhosis and jaundice.
The half-life of chloramphenicol reaches up to 28 hours in infants with very few days of life.

5.3 Preclinical safety data
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. In fact, chloramphenicol was shown to be genotoxic in human and murine cells only at concentrations 25 times higher than the maximum dose used in humans.
In chicken embryos, chloramphenicol inhibits growth and rarely causes splanchnopleure and neural tube defects. In rat experiments, exposure to a diet containing 2-4% chloramphenicol during the last stage of gestation caused only oedema in foetuses. No other congenital anomalies were detected in further teratogenicity studies conducted in rats, rabbits and monkeys.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
None.

6.2 Incompatibilities
Chloramphenicol Fisiopharma should not be mixed with the following medicines:
- chlortetracycline
- novobiocin sodium

The following incompatibilities with chloramphenicol have also been reported:
- chlorpromazine;
- erythromycin;
- fluconazole;
- glycopyrrolate;
- hydrocortisone sodium succinate;
- hydroxyzine;
- methicillin;
- methochlopramyde;
- oxytetracycline;
- phenytoin;
- polymyxin B;
- procaine;
- prochlorperazine edisylate;
- prochlorperazine mesylate;
- promazine;
- promethazine;
- sulfadiazine;
- tetracyclines;
- tripelennamine;
- vancomycin.

6.3 Shelf life
In intact package: The expiry date of the product is indicated on the packaging materials.
After reconstitution: The reconstituted solution must be injected immediately.

6.4 Special precautions for storage
Store below 25°C.

6.5 Nature and contents of container
Chloramphenicol Fisiopharma 1 g powder for solution for injection is packaged in transparent glass vials, with chlorobutyl rubber stoppers and closed with flip-off caps. The package contains 10 vials with 1 g of chloramphenicol each.

6.6 Special precautions for disposal and handling
The unused drug and waste material derived from this drug should be disposed of according to the local rules in force.

7. MANUFACTURER
FISIOPHARMA S.R.L Nucleo Industriale – 84020 Palomonte (SA), Italy

8. MARKETING AUTHORISATION HOLDER
Propharm LTD POB 4046, Zichron Yaacov 30900

9. MARKETING AUTHORISATION NUMBER
165-65-35172-00

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