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).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection for intravenous use.

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

Chloramphenicol Fisiopharma is for intravenous use. The following dosages are recommended:

Adults and adolescents

The recommended dose for the treatment of most infections is 50-100 mg/kg/day divided in 4 daily doses (1 dose every 6 hours).

Infants up to 2 weeks

The recommended dose for the treatment of most infections is 25 mg/kg/day divided in 4 daily doses (1 dose every 6 hours).

For infants up to 1 week or weighing less than 2 kg, the recommended dose is 25 mg kg/day every 24 hours (once daily).

For infants over 1 week and weighing more than 2 kg, the recommended dose is 25 mg/kg/day divided in 2 daily doses (1 dose 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 in 4 daily doses (1 dose every 6 hours).

Impaired renal function

Although chloramphenicol does not significantly accumulate in presence of impaired renal function, the affected patients may have reduced ability to eliminate the drug and may require a dosage adjustment. Concentration of the drug in the blood should be frequently monitored to establish if the dosage adjustment is necessary.

Impaired hepatic function

Patients with impairment of hepatic function may have reduced ability to eliminate the drug and the dosage adjustment may be required. Concentration of the drug in the blood should be monitored to establish if the dosage adjustment is necessary.

In patients with impaired hepatic function, a loading dose of 1 g followed by 500 mg every 6 hours is recommended. Dosage of 500 mg every 6 hours is recommended in patients with liver cirrhosis.

In patients with jaundice, the dosage of 25 mg/kg/day must not be exceeded.

Patients on dialysis

The amount of drug removed by hemodialysis cannot justify a dosage adjustment in all cases.

The dosage should not be adjusted in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) or continuous arteriovenous haemofiltration (CAVH).

The solution for injection should be prepared extemporaneously by dissolving the powder in water for injections, saline or a 5% glucose solution, at the desired concentrations.

4.3 Contraindications

- Hypersensitivity to active substance or to any of the excipients;
- Bone marrow depression;
- Breastfeeding (see the section 4.6).

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

Chloramphenicol may interfere with the immunity mechanisms and must not be administered during the phase of active immunization (see section 4.5).

4.4 Special warnings and precautions for use

Treatment with the antibiotic should not be continued longer than the period indicated by the specific recommendation for each infection, possibly no longer than 2 weeks. Close monitoring of the blood levels during the treatment is recommended.

Administration of chloramphenicol in high dosages and for prolonged and repeated courses may cause the onset of aplastic anemia that may be detected weeks or months after the treatment discontinuation.

Chloramphenicol must be used with great caution in patients with blood dyscrasias. In prolonged or repeated treatment, the blood should be frequently monitored and the treatment should be interrupted immediately if the leukocytes drop below 4000 per mm3 and the granulocytes decrease by 40% (unless it is an inherent leukopenic infection such as fever typhoid); late complications are possible.

The use of chloramphenicol may also lead to a decrease in prothrombin time due to the inhibition of the intestinal flora producing vitamin K.

In patients with hepatic or renal insufficiency, 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 due to insensitive bacterial agents or fungi.

4.5 Interaction with other medicinal products and other forms of interaction

Chloramphenicol is an inhibitor of P450 cytochrome that may increase the half-life of various drugs with a consequent increase of their toxicity. Chloramphenicol decreases the metabolism of the following drugs:

- dicumarol and warfarin;
- phenytoin and fosphenytoin;
- clopidogrel;
- voriconazole;
- cyclophosphamide;
- cyclosporine;
- tacrolimus;
- phenobarbital;
- rifampicin.

Chloramphenicol may also interact with the following drugs:

- paracetamol: it may cause an increase in the toxicity of chloramphenicol;

- beta-lactam antibiotics (penicillins and cephalosporins): antagonism with chloramphenicol may occur;
- cyanocobalamine: chloramphenicol may decrease the effect of cyanocobalamine;
- entacapone: chloramphenicol may cause a reduction in the biliary excretion of entacapone with a consequent increase of toxicity;
- hypoglycemic sulfonamides (tolbutamide, chlorpropamide, glimepiride etc.): chloramphenicol may cause an excessive hypoglycemic response;
- iron: chloramphenicol decreases the effectiveness of iron;
- methotrexate: chloramphenicol, by inhibiting the intestinal bacterial flora, decreases the intestinal absorption of methotrexate.

Furthermore, chloramphenicol may interfere with immune mechanism and should not be administered during the active immunization phase, such as with tetanus toxoid or live typhoid vaccine.

Chloramphenicol may give a false positive result in the test that uses 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 obtained with a large number of exposed pregnancies indicate no particular undesirable effects of chloramphenicol in pregnancy and on the health of the fetus/newborn, with the exception of the final stages of pregnancy, during which “gray baby syndrome” may occur, sometimes even fatal (see section 4.8). Therefore, chloramphenicol should not be used during pregnancy unless absolutely necessary.

Breastfeeding

Chloramphenicol is excreted in breast milk. Although chloramphenicol concentrations are probably too low to induce “gray baby syndrome” (see section 4.8), this risk cannot be completely excluded. In addition, bone marrow depression or other serious adverse effects in the infant may occur. Therefore, chloramphenicol should not be administered during breastfeeding.

4.7 Effects on ability to drive and use machines

Chloramphenicol Fisiopharma does not affect the ability to drive or use machines.

4.8 Undesirable effects

The following are the undesirable effects of chloramphenicol categorised according to the MedDRA system organ class. Insufficient data are available to establish the frequency of the individual effects listed.

Disorders of the blood and lymphatic system

Bone marrow depression: it may occur in two different forms: the first, dose-dependent form is characterised by agranulocytosis, anemia, leukopenia, thrombocytopenia and reticulocytopenia; the second form that is not dose- related, is a very severe form of aplastic anemia that develops after a latent period of weeks or even months.

Depression of erythropoiesis is more frequent in patients with hepatic or renal insufficiency.

Traumatism, poisoning and procedural complications

“Gray baby syndrome”: this toxic manifestation has been observed in newborns who have been given high doses of chloramphenicol. It is characterised by abdominal distension, vomiting, ashy skin, hypothermia, progressive cyanosis, circulatory collapse, and death within hours or days. It appears that the cause may be the lack of glucuronide conjugation of chloramphenicol, due to inadequate hepatic glucuronyltransferase activity during the first weeks of neonatal life, and inadequate renal excretion of the unconjugated drug.

Gastrointestinal disorders

Nausea, vomiting, unpleasant taste sensation (dysgeusia), diarrhea, stomatitis, glossitis, enterocolitis, perineal irritation.

Disorders of the immune system

Hypersensitivity reactions with the onset of fever, rash, anaphylaxis.

Nervous system disorders

Optic or peripheral neuritis, ototoxicity, headache, mental confusion.

Infections and infestations

Jarisch-Herxheimer reaction, characterised by chills, headache, fever and mucocutaneous lesions.

Psychiatric disorders

Mild depression and delirium

Respiratory, thoracic and mediastinal disorders

Bronchospasm

Hepatobiliary disorders

Hepatotoxicity

Reporting of side effects

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

Overdose increases the risk of complications especially haematological complication related to the direct toxicity of chloramphenicol (see section 4.8 Undesirable effects).

Chloramphenicol is only partially removed from the blood by peritoneal dialysis or hemodialysis. In infants, both full blood transfusions and charcoal haemoperfusion were used for chloramphenicol overdoses.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use; ATC code: J01BA01

Chloramphenicol is a broad-spectrum antibiotic. 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 also that of eukaryotic cells. It acts by reversibly binding to the 50S subunit of the bacterial ribosome, thus inhibiting protein synthesis.

The generally sensitive microbial species (CMI 5 g / 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); Rickettsial, Mycoplasma, Chlamydiae. The microbial species that are not always sensitive: Staphylococci, Enterococci, Colibacilli, Klebsiella, Proteus.

On the other hand, the following species are resistant (CMI 25 g / ml): Serratia, Acinetobacter, Pseudomonas.

The main mechanism of bacterial chemoresistance to chloramphenicol for gram-negative species consists in the enzymatic acetylation of the molecule, mediated by an R factor. 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 case of salmonella, resistance extends to tetracyclines, streptomycin and sulfonamides. Cross-resistance to thiamphenicol may occur. Pseudomonas aeruginosa and some strains of Proteus and Klebsiella resist chloramphenicol with a non-enzymatic mechanism which includes an inducible blocking of permeability.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

Chloramphenicol spreads rapidly, however its distribution is not uniform. The highest concentrations are found in the liver and kidney; the lowest concentrations are found in the brain and cerebrospinal fluid. Chloramphenicol penetrates into the cerebrospinal fluid even in the absence of the meninx inflammatory state and reaches concentrations about half of those found in the blood. Measurable levels are also detected in pleural and ascitic fluids, saliva, milk, and aqueous and vitreous humors. Furthermore, chloramphenicol crosses the placental barrier.

The volume of distribution is 0.5-1 l/kg.

50%-80% of the dose is bound to plasma proteins.

Metabolism

Chloramphenicol is rapidly metabolised at hepatic level, mostly in derivates with glucuronic acid, microbiologically inactive, which are rapidly excreted by the kidney. It should be taken into consideration that in neonates the capacity for glucuronidation and renal elimination is very limited.

Elimination

Chloramphenicol is mainly excreted in the urine (90%) as a conjugate of glucuronic acid and, in a small amount, in unchanged form. Small amounts are excreted in bile (2-3%) and in faeces (1%).

The plasma half-life varies from 1.5 to 5 hours.

In patients with kidney impairment, the half-life varies from 3 to 7 hours.

In patients with 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 newborns with very few days of life.

5.3 Preclinical safety data

In non-clinical studies, effects at exposure were only observed since considered significantly higher than the maximum human exposure; however, this has insignificant clinical relevance. In fact, chloramphenicol has been shown to be genotoxic in human and mouse cells only at concentrations 25 times higher than the maximum dose used in humans.

In chicken embryos, chloramphenicol inhibits growth and rarely leads to splanchnopleural and neural tube defects. In experiments with rats, exposure to a diet containing 2-4% of chloramphenicol during the last phase of gestation only caused edema in the fetuses. No other congenital anomalies were detected in additional teratogenic studies conducted in rats, rabbits and monkeys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Chloramphenicol Fisiopharma must not be mixed with the following medicinal products:

- chlorotetracycline;
- sodium novobiocin.

The following incompatibilities with chloramphenicol have also been reported:

- chlorpromazine;
- erythromycin;
- fluconazole;
- glycopyrrolate;
- hydrocortisone sodium succinate;
- hydroxizine;
- methicillin;
- metoclopramide;
- 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 should be injected immediately.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Package of Chloramphenicol Fisiopharma 1 g contains 10 vials with 1 g of powder each.

6.6 Special precautions for disposal and handling

Unused medicine and waste derived from this medicine must be disposed of in accordance with local regulations.

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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