NATIONAL AGENCY FOR FOOD & DRUG ADMINISTRATION & CONTROL (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

Product Name

CHLORAMPHENICOL SODIUM SUCCINATE FOR INJECTION BP 1 gm

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

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SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. Name of the Medicinal Product

Chloramphenicol Sodium Succinate for Injection BP 1 gm

2. Qualitative and Quantitative Composition

Each vial contains:

Chloramphenicol sodium Succinate BP

eq. to Chloramphenicol 1 gm

3. Pharmaceutical Form

Dry Powder Injection

4. Clinical Particulars

4.1 Therapeutic indications

Chloramphenicol is an antibiotic that is clinically useful for, *and should be reserved for,* serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists

4.2 Posology and method of administration

Dosage and Administration

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract. In controlled studies in adult volunteers using the recommended dosage of 50 mg/kg/day, a dosage of 1 g every 6 hours for 8 doses was given. Using the microbiological assay method, the average peak serum level was 11.2 mcg/mL one hour after the first dose. A cumulative effect gave a peak rise to 18.4 mcg/mL after the fifth dose of 1 g. Mean serum levels ranged from 8 to 14 mcg/mL over the 48-hour period. Total urinary excretion of chloramphenicol in these studies ranged from a low of 68% to a high of 99% over a three-day period. From 8% to 12% of the antibiotic excreted is in the form of free chloramphenicol; the remainder consists of microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most chloramphenicol detected in the blood is in the microbiologically active free form. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol is relatively high, amounting to several hundred mcg/mL in patients receiving divided doses of 50 mg/kg/day. Small amounts

of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. Measurable levels are also detected in pleural and in ascitic fluids, saliva, milk, and in the aqueous and vitreous humors. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of neonates than in maternal blood.

4.3 Contraindications

The information in this database is intended to supplement, not substitute for, the expertise and judgment of healthcare professionals. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for you or anyone else. A healthcare professional should be consulted before taking any drug, changing any diet or commencing or discontinuing any course of treatment.

4.4 Special warning and special precaution for use

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents

4.5 Interaction with other medicinal products and form of interaction

Chloramphenicol has no known severe interactions with other drugs.

Serious interactions of chloramphenicol include:

Lurasidone

Serious interactions of chloramphenicol include:

BCG vaccine live

cefoxitin

cholera vaccine

mefloquine

red yeast rice

typhoid vaccine live

vilazodone
warfarin
Moderate interactions of chloramphenicol include:
axitinib
bazedoxifene/conjugated estrogens
ceftriaxone
conjugated estrogens, vaginal
eluxadoline
estradiol
estrogens conjugated synthetic
estrogens esterified
estropipate
fosphenytoin
ivacoftor
lomitapide
maraviroc
mestranol
ospemifene
phenytoin
piperacillin
sodium picosulfate/magnesium oxide/anhydrous citric acid
Chloramphenicol has minor interactions with 47 different drugs.

4.6 Pregnancy and lactation

Safety has not been established during pregnancy.
-According to some authorities: Use is contraindicated.
-According to some authorities: Use should be avoided during the week before parturition.
-According to some authorities: This drug should be used during pregnancy only if the benefit outweighs the risk to the fetus.
AU TGA pregnancy category: A
US FDA pregnancy category: C
Animal studies have not been reported. There are no controlled data in human pregnancy.
Oral chloramphenicol crosses the placenta. While there are no literature reports linking the use of this drug in pregnancy to birth defects, use late in pregnancy has been associated with adverse effects in the neonate (i.e., grey baby syndrome).

AU TGA pregnancy category A: Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

US FDA pregnancy category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

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. 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 longterm 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.

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.

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

Absorption:

With I.V. administration, serum levels vary greatly, depending on patient's metabolism.

Distribution:

Distributed widely to most body tissues and fluids, including CSF, liver, and kidneys; it readily crosses the placental barrier. About 50% to 60% of drug binds to plasma

proteins.

Metabolism:

Parent drug is metabolized primarily by hepatic glucuronyl transferase to inactive metabolites.

Excretion:

About 8% to 12% of dose is excreted by the kidneys as unchanged drug; the remainder is excreted as inactive metabolites. Plasma half-life ranges from about 1 1/2 to 4 1/2 hours in adults with normal hepatic and renal function. Plasma half-life of parent drug is prolonged in patients with hepatic dysfunction. Peritoneal hemodialysis doesn't remove significant drug amounts. Plasma chloramphenicol levels may be elevated in patients with renal impairment after I.V. chloramphenicol administration.

5.3 Preclinical Studies

Inter-individual variation exists in determining the pharmacokinetics for a given patient with impaired and/or immature hepatic or renal function. 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.

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6.0 PHARMACEUTICAL EXCIPIENTS

6.1 List of excipients

Not applicable

6.2 Incompatibilities

None known

6.3 Shelf life

24 Months

6.4 Special precaution for storage

Store below 30°C. Protect from light.

6.5 Nature contents of container

10 ml glass vial

6.6 Instruction for use handling and disposal

Keep out of reach of children.

7. Manufacturer name

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8. Marketing Authority

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