Brand Name : AGOPHENOL SUSPENSION **Generic Name :** Chloramphenicol Oral Suspension		2021
Module 1 **1.5**	Administrative Information and Product Information Product Information	**Confidential**

1.5 PRODUCT INFORMATION

1.5.1 Prescribing information (Summary of products characteristics)

SUMMARY PRODUCT CHARACTERISTICS

1. Name of drug product:

AGOPHENOL SUSPENSION (Chloramphenicol Oral Suspension)

2. Qualitative and Quantitative Composition:

Each 5 ml contains: Chloramphenicol Palmitate BP eq. to 125 mg of Chloramphenicol

3. Pharmaceutical form:

White thick uniform suspension on shaking.

4. Clinical particulars:

4.1 Therapeutic indications

Chloramphenicol is a synthetically manufactured broad-spectrum antibiotic. It was initially isolated from the bacteria *Streptomyces venezuelae* in 1948 and was the first bulk produced synthetic antibiotic.[1] However, chloramphenicol is a rarely used drug in the United States because of its known severe adverse effects, such as bone marrow toxicity and grey baby syndrome.

Indications for its use include superficial eye infections (bacterial conjunctivitis), and otitis externa. It is also reserved for severe infections, such as rickettsial diseases, meningitis caused by *Haemophilus Influenza, Neisseria meningitidis, or Streptococcus pneumoniae,* or in typhoid fever caused by *Salmonella enterica serotype Typhi.*[2][3][4][5] It can also be used for the treatment of cholera.[6]

Chloramphenicol ointments are also used perioperatively as prophylaxis for surgical wound infections. This therapy is often necessary for plastic surgery and eye surgery.[7][8]

However, despite these indications, chloramphenicol should only be initiated if there is known susceptibility to the drug, and when other less dangerous antimicrobials are ineffective, not tolerated or contraindicated. Moreover, in vitro sensitivity tests have to be

done to discontinue the medication as soon as other less dangerous antimicrobials demonstrate therapeutic effectiveness.

4.2 Posology and method of administration

Chloramphenicol can be administered topically as eye or ear drops, or as an eye ointment. It can also be given parenterally as intravenous injection or infusion or taken as oral Suspension. Due to its high risk of adverse effects and toxicity, clinicians should prescribe chloramphenicol at therapeutic doses of not more than 50 mg/kg/day, given in divided doses at 6-hourly intervals. This dose may require an increase to 100 mg/kg/day for severe infections caused by moderately resistant organisms. If such increment in dosage is required, careful monitoring is imperative, with dose reductions back to 50mg/kg/day made as soon as possible. Also, dose reductions to 25 mg/kg/day may be necessary for neonates, and patients who have impaired liver or renal function.

If administered as an intravenous infusion, it has to be given intermittently and diluted in either 0.9% sodium chloride or 5% glucose solutions.

Clinicians should avoid using prolonged treatment with chloramphenicol.

4.3 Contraindications

Acute porphyria is an absolute contraindication to the use of chloramphenicol. Additionally, any known hypersensitivity to chloramphenicol, such as any previous anaphylactic reactions to the drug, should warrant the use of other antimicrobials. Signs of anaphylactic reaction to the medication include angioedema, bronchospasm, and urticaria. Delayed onset hypersensitivity reactions such as contact dermatitis have also been reported. This reaction often presents 24 to 72 hours after the application of the medication with swelling and erythema.

Moreover, due to the potential risk of toxicity to neonates, chloramphenicol should also not be prescribed in neonates less than one week old, especially preterm infants. Currently, it is classed as a pregnancy category C drug and should be avoided in pregnancy or breastfeeding. However, there have been studies that show no associated teratogenicity with chloramphenicol use during the first trimester of pregnancy.

4.4 Toxicity

Chloramphenicol can be fatal in an overdose; this usually occurs with intravenous administration of the drug and is more likely to affect infants. Symptoms of poisoning include nausea and vomiting, abdominal distension, metabolic acidosis, hypotension, hypothermia, cardiovascular collapse, and coma.

Grey baby syndrome is a well-known condition that arises from chloramphenicol toxicity in infants, especially affecting preterm neonates. It can also affect breastfed infants whose mothers are taking oral chloramphenicol.[31] A preterm neonate is more likely to be affected as their immature liver is unable to produce enough UDP-glucuronyltransferase enzyme needed to metabolize chloramphenicol, by glucuronidation, for renal excretion. The resultant accumulation of chloramphenicol in the infant will lead to gray baby syndrome. Symptoms of the grey baby syndrome vary depending on the serum concentration of the drug in the body.

Examples of signs and symptoms of toxicity include poor feeding, irritability, abdominal distension, vomiting, grey skin discoloration, and sudden collapse from cardiovascular and respiratory complications.[32][33][34] Due to the possible risk of fatality associated with chloramphenicol exposure in neonates, an alternative drug should always be considered for breastfeeding mothers. However, if chloramphenicol is the therapeutic choice, close monitoring of the infant is required

4.5 Mechanism of Action

EFChloramphenicol is bacteriostatic but can be bactericidal in high concentrations. It is a broad-spectrum antibiotic be used against Gram-positive, Gram-negative, and anaerobic bacteria.[9][10] Chloramphenicol works by inhibiting protein synthesis by binding to the 50S ribosomal subunit and directly preventing the formation of bacterial protein.[11] Other antibiotics that also target the 50S ribosomal subunit include clindamycin (a lincosamide) and macrolides such as erythromycin and clarithromycin. However, these drugs work differently. On a molecular level, chloramphenicol inhibits the attachment of transfer RNA to the A site on the 50S ribosome. In contrast, lincosamides act on the A and P sites, whereas macrolides block the tunnel through which nascent peptides exit.

4.6 Fertility, pregnancy and lactation

A: Generally acceptable. Controlled studies in pregnant women show no evidence of fetal risk.
B: May be acceptable. Either animal studies show no risk but human studies not available or animal studies showed minor risks and human studies done and showed no risk.
C: Use with caution if benefits outweigh risks. Animal studies show risk and human studies not available or neither animal nor human studies done.
D: Use in LIFE-THREATENING emergencies when no safer drug available. Positive evidence of human fetal risk.
X: Do not use in pregnancy. Risks involved outweigh potential benefits. Safer alternatives exist.
NA: Information not available.

4.7 Adverse effects

Chloramphenicol is associated with severe hematological side effects when administered systemically. Since 1982, chloramphenicol has reportedly caused fatal aplastic anemia, with possible increased risk when taken together with cimetidine. This adverse side effect can occur even with the topical administration of the drug, which is most likely due to the systemic absorption of the drug after topical application.

There are two different types of chloramphenicol-induced blood dyscrasias. The first type is more common and is predictable, dose-related, and reversible. It causes mild anemia, with thrombocytopenia and neutropenia. The second form is an idiosyncratic reaction that has a later onset and is more likely to be fatal after pancytopenia develops. This type is unpredictable, irreversible, and dose-independent. Aplastic anemia appears to occur as a result of chloramphenicol's effect on depleting ferritin concentrations in the mitochondria

because of the shared ribosomal structures between bacteria and mitochondria, making the latter susceptible to the drug's ability to inhibit protein synthesis within the mitochondria. There have also been cases of leukemia developing after aplastic anemia from chloramphenicol use.

Besides causing fatal aplastic anemia and bone marrow suppression, other side effects of chloramphenicol include ototoxicity with the use of topical ear drops, gastrointestinal reactions such as oesophagitis with oral use, neurotoxicity, and severe metabolic acidosis.

Optic neuritis is the most commonly associated neurotoxic complication that can arise from chloramphenicol use. This adverse effect usually takes more than six weeks to manifest, presenting with either acute or subacute vision loss, with possible fundal changes. It may also present with peripheral neuropathy, which may present as numbness or tingling. If optic neuropathy occurs, the drug should be withdrawn immediately, which will usually lead to partial or complete recovery of vision

5. Pharmacological properties

5.1 Pharmacology properties

Distribution: to most tissues & body fluids; readily crosses placenta; enters breast milk CSF: blood level ratio: normal meninges: 66%; inflamed meninges: >66%
Protein Bound: 60%

Half-life Elimination

Normal renal function: 1.6-3.3 hr
End-stage renal disease: 3-7 hr
Cirrhosis: 10-12 hr

Excretion

Urine: 5-15%
Feces: 4%

Other Information

Metabolism: extensively hepatic (90%) to inactive metabolites, principally by glucuronidation; chloramphenicol palmitate is hydrolyzed by lipases in GI tract to the active base; chloramphenicol sodium succinate is hydrolyzed by esterases to active base

6. Pharmaceutical particulars:

6.1 List of Excipients:

Sorbitol 70%	BP
Methyl Paraben Sodium	BP
Propyl Paraben Sodium	BP
Carboxyl Methyl Cellulose Sodium (HVP)	BP
Sodium Citrate	BP
Citric Acid Monohydrate	BP
Sodium Benzoate	BP

Essence Orange Sweet No.1	INH
Sucrose	BP
Propyl sorbate (Tween-80)	BP
Propylene Glycol	BP

6.2 Incompatibilities:
None Reported

6.3 Shelf-Life:
36 months from the date of manufacture.

6.4 Special Precautions for Storage:
Store under normal storage conditions (15ºC-30ºC) Protect from light.

6.5 Nature and Contents of Container:
100 ml suspension filled in one bottle. Such bottle packed in carton with pack insert. Such carton packed and export in worthy shipper.

6.6 Special precautions for disposal:
None reported.

7. Registrant:
AGOG PHARMA LTD.
Plot No. 33, Sector II,
The Vasai Taluka Industrial
Co-Op. Estate Ltd., Gauraipada,
Vasai (E), Dist. Thane,
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9. Date of revision of the text: