1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1.3.1.1 NAME OF THE MEDICINAL PRODUCT

International Non– Proprietary Name (INN): DUBAN (Chloramphenicol Sodium Succinate for injection BP 1g)

1.3.1.2 ATC AND FORENSIC CLASSIFICATION

ATC Classification: Antibacterials for systemic use. Amphenicols.

ATC Code: ATC code: J01BA01

1.3.1.3 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Vial Contains
Chloramphenicol sodium Succinate BP
eq. to Chloramphenicol .....1 gm

1.3.1.4 PHARMACEUTICAL FORM

Powder for Injection.
White or yellowish-white powder, hygroscopic filled in 10ml clear glass vial USP T-III.

1.3.1.5 CLINICAL PARTICULARS

1.3.1.5.1 Therapeutic Indications

Chloramphenicol 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.

1.3.1.5.2 Posology and Method of Administration

Posology:

The dose administered and the concentration used is dependent on the severity of the infection. The recommended standard dosage is as follows:
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.
Neonates and Premature Infants: 25 mg/kg in divided doses. Only 10% or lower concentrations to be used. The 10% solution can be prepared by extracting 5ml of the 20% solution and adding 5ml of diluent (Water for Injections, Sodium Chloride Injection or Dextrose Injection 5%) under

aseptic conditions. The 10 % solution should be given by intravenous injection over a period of about a minute, or in a larger volume of fluid, by slow intravenous infusion. The concurrent administration of intravenous Chloramphenicol with topical treatment has been found to be very effective in the treatment of osteomyelitic foci, abscesses, empyema and skin and urinary infections.

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 or intramuscular injection.

In order to ensure rapid attainment of high blood levels, Chloramphenicol is best administered by intravenous injection. Where this is not possible, however, intramuscular administration may be used, although it should be borne in mind that absorption may be slow and unpredictable.

The injection should be reconstituted with Water for Injections, Sodium Chloride Injection, or Dextrose Injection 5 %. The following dilution table may be useful for the administration of a proportion of the contents of a vial:

Concentration	Solution strength	Volume of diluent to be added	Total volume after dilution
40%	400 mg/ml	1.7 ml	2.5 ml
25%	250 mg/ml	3.2 ml	4.0 ml
20%	200 mg/ml	4.2 ml	5.0 ml

1.3.1.5.3 Contraindications

Chloramphenicol is contraindicated in patients with a previous history of sensitivity and/or toxic reaction to chloramphenicol.

1.3.1.5.4 Special warnings and precautions for use

Chloramphenicol 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. Chloramphenicol should not be used for trivial infections due to the possibility of severe blood dyscrasias, which may prove fatal.

<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. (See section 4.8) 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 hospitalized 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.

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 summarizes 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 nonsusceptible organisms, including fungi. If infections caused by nonsusceptible 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 diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
Effects on immunity
Chloramphenicol may also impede the development of immunity and should therefore not be given during active immunisation.
Sodium
This medicinal product contains 71.2 mg sodium per vial, equivalent to 3.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

1.3.1.5.5 Interaction with other medicinal products and other forms of interaction

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 be necessary. Plasma concentrations of chloramphenicol may be reduced with concomitant usage of phenobarbital and rifampicin

1.3.1.5.6 Pregnancy and lactation

The use of chloramphenicol is contraindicated in pregnancy and whilst breastfeeding.

1.3.1.5.7 Effects on ability to drive and use machines

Chloramphenicol has no or negligible influence on the ability to drive and use machines.

1.3.1.5. Undesirable effects

Tabulated summary of adverse reactions

The adverse reactions are grouped according to their system organ classes and the frequencies ranked according to the following convention: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)	Not known (cannot be estimated from the available data)
Infections and infestations						Fungal superinfection
Blood and lymphatic system disorders					Aplastic anaemia	Agranulocytosis Bone marrow failure Pancytopenia Thrombocytopenic purpura
Psychiatric disorders						Depression
Nervous system disorders						Peripheral neuritis Headache
Eye disorders						Optic neuritis
						Transient blindness Blurred vision
Cardiac disorders						Neonatal Grey syndrome
Gastrointestinal disorders						Vomiting Diarrhoea Nausea Dry mouth
Skin and subcutaneous tissue disorders						Urticaria

Bone marrow depression and blood disorders

Chloramphenicol may cause severe bone marrow depression which may lead to serious and potentially fatal blood dyscrasias, such as agranulocytosis, thrombocytopenic purpura or aplastic anaemia

Paediatric population

Grey syndrome is a serious adverse effect that has been reported in neonates and infants following the intravenous administration of chloramphenicol.

1.3.1.5.9 Overdose

Levels exceeding 25 mcg/ml are frequently considered toxic.

Symptoms

Chloramphenicol toxicity can be evidenced by serious haemopoietic effects such as aplastic anaemia, thrombocytopenia, leucopenia, as well as increasing serum iron levels, nausea, vomiting and diarrhoea.

Management

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.

1.3.1.6 PHARMACOLOGICAL PROPERTIES

1.3.1.6.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use. Amphenicols.
ATC code: J01BA01

1.3.1.6.2 Pharmacokinetic properties

Absorption

After intravenous administration steady state peak concentrations were reached on average 18.0 minutes after cessation of the infusion.

Distribution

Chloramphenicol is widely distributed in body tissues and fluids and enters the cerebrospinal fluid.

Biotransformation

After administration chloramphenicol is rapidly released from Chloramphenicol sodium succinate. Chloramphenicol sodium succinate, free chloramphenicol and metabolites are excreted in the urine.

Elimination

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

Paediatric population

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

1.3.1.6.3 Preclinical safety data

Nothing of relevance which is not included in other sections of the SPC.

1.3.1.7 PHARMACEUTICAL PARTICULARS

1.3.1.7.1 Incompatibilities

Not Known

1.3.1.7 2 Shelf life

36 Months

1.3.1.7.3 Special precautions for storage

Store at below 30°C at dry place, protected from light.

1.3.1.7.4 Nature and contents of container

White or yellowish-white powder, hygroscopic filled in 10ml clear glass vial USP T-III.

1.3.1.7.5 Special precautions for disposal

Store at below 30°C at dry place after opening.

1.3.1.8 Registrant/Manufacturer

APPLICANT

M/s. Maydon Pharmaceuticals Limited,
15 Wilmer Street, Off Town Planning Way,
Ilupeju, Lagos, Nigeria

MANUFCTURER

Nitin Lifesciences Ltd. (Unit – III)
Rampur Road, Paonta Sahib
Dist. Sirmour-173025,
Himachal Pardesh, India.