1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed

ARTESUNATE FOR INJECTION (COMBIPACK) RRBOK		
MODULE I :	**ADMINISTRATIVE PARTICULARS OF THE PRODUCT**	
Document	**1.3**	**Product Information**

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

(A) ARTESUNATE INJECTION 120 MG

1. Name of the medicinal product

1.1 (Invented) Name of the medicinal product
ARTESUNATE INJECTION 120 MG

1.2 Strength
Each Vial Contains:
Artesunate 120 mg

1.3 Pharmaceutical Form
Powder for injection

2. Qualitative and Quantitative Formula
Batch Size: 4.5 Kg

Sr. No.	Name of Ingredient	Quantity/ Vial (mg)	Quantity/Batch (Kg)	Functions
1.	Artesunate BP	120.000	4.500	Antimalarial

3. Pharmaceutical form
White colour powder.

4. Clinical particulars
4.1 Therapeutic Indication:
ATRESUNATE, administered intravenously or intramuscularly, is indicated for the treatment of severe malaria caused by Plasmodium falciparum, in adults and children.

4.2 Posology and method of administration:
Dose:
Adults and children: Atresunate is administered at a dose of 2.4 mg of artesunate / kg body weight, by intravenous (IV) or intramuscular (IM) injection, at 0, 12 and 24 hours, then once daily until oral treatment can be substituted.
Atresunate should be administered for a minimum of 24 hours (3 doses), regardless of the patient's ability to tolerate oral medication earlier. After at least 24 hours of **Atresunate**, and when able to tolerate oral medication, the patient should be switched to a complete treatment course of an oral combination antimalarial regimen. Relevant treatment guidelines should be consulted when selecting an appropriate regimen (e.g. those of the WHO: http://www.who.int/malaria/en/).
Preparation
Because of the instability of artesunate in aqueous solutions the reconstituted solution must be used within one hour of preparation. Therefore the required dose of artesunate should be calculated (dose in mg = patient's weight in kg x 2.4) and the number of vials of artesunate

Reconstitution of the artesunate solution

Using a syringe, withdraw 1 ml of the supplied sodium bicarbonate solvent from the ampoule and inject into the vial containing the artesunate powder. Shake the vial for several minutes to mix well until the powder is completely dissolved and the solution is clear. If the solution appears cloudy or a precipitate is present, it should be discarded. The reconstituted artesunate solution should always be used immediately, and discarded if not used within one hour.

Following reconstitution the solution must be diluted according to the method of injection, as described below.

For intravenous (IV) injection

Using a syringe, add 5 ml of sodium chloride 0.9% for injection to the vial containing the reconstituted artesunate solution. This will yield 6 ml of a solution containing artesunate 10 mg/ml. Shake to mix well, ensuring that the resulting solution is still clear. If the solution appears cloudy or a precipitate is present, it should be discarded.

The volume required will be equal to: $\frac{\text{(desired dose in mg)}}{10}$ ml

Withdraw the required volume of artesunate solution from the vial with a syringe and then inject slowly intravenously, the speed of IV consistent with slow bolus: 3-4 ml/min.

Atresunate should NOT be administered as an intravenous drip.

For intramuscular (IM) injection

Using a syringe, add 2 ml of sodium chloride 0.9% for injection to the vial containing the reconstituted artesunate solution. This will yield 3 ml of a solution containing artesunate 20 mg/ml. Shake to mix well, ensuring that the resulting solution is still clear. If the solution appears cloudy or a precipitate is present, it should be discarded.

The volume required will be equal to: $\frac{\text{(desired dose in mg)}}{20}$ ml

Withdraw the required volume of artesunate solution from the vial with a syringe and then inject intramuscularly; the anterior thigh is usually the preferred site for injection. If the total volume of solution to be injected intramuscularly is large, it may be preferable to divide the volume and inject it at several sites, e.g. both thighs.

Do not use water for injection for reconstitution of the artesunate powder or for dilution of the resulting solution prior to injection.

Hepatic and renal impairment:

Dose adjustment is not necessary in patients with hepatic or renal impairment (see Sections 4.4 and 5.2).

4.3 Contraindications:

Atresunate is contraindicated in patients with hypersensitivity to artesunate or other artemisinins.

4.4 Special warnings and precautions for use:

Non-falciparum malaria

Artesunate has not been evaluated in the treatment of severe malaria due to Plasmodium vivax, Plasmodium malariae or Plasmodium ovale.

Switching to oral treatment regimen

Acute treatment of severe falciparum malaria with Artesun® should always be followed by a complete treatment course of an appropriate oral combination antimalarial regimen (see Section 4.2)

Resistance to antimalarials

Local information on the prevalence of resistance to antimalarials should be considered in choosing the appropriate combination antimalarial regimen for use with Artesun®. Relevant treatment guidelines should be consulted (e.g. those of the WHO: http://www.who.int/malaria/en/).

Post-treatment anaemia

Despite transient decreases in reticulocyte counts, clinically significant anaemia associated with IV artesunate has not been common in clinical trials. However, occasional cases of post-treatment haemolytic anaemia severe enough to require transfusion have been reported (see Section 4.8).

Hepatic / renal impairment:

Data regarding artesunate pharmacokinetics in patients with hepatic and/or renal impairment are limited. Based on data from studies in patients with severe malaria, as well as the known metabolism of artesunate (see Section 5.2), dosage adjustment is not considered necessary in patients with hepatic or renal impairment.

Paediatric population

In clinical trials, the efficacy and safety of intravenous and intramuscular artesunate have been similar in adult and paediatric populations.

4.5 Interaction with other medicinal products and other forms of interaction:

Artesunate is rapidly and extensively converted to dihydroartemisinin (DHA), the active metabolite, primarily by plasma and erythrocyte esterases. DHA elimination is also rapid (half-life approximately 45 min) and the potential for drug-drug interactions appears limited. In vitro drug-interaction studies have demonstrated minimal effects of artesunate on cytochrome P450 isoenzymes. Few clinical drug-drug interaction studies have been performed, however no clinically significant interactions have been identified.

4.6 Fertility, Pregnancy and lactation:

Pregnancy

Severe malaria is especially hazardous during pregnancy, therefore full dose parenteral antimalarial treatment should be administered without delay.

There has been limited clinical experience with the use of artesunate in pregnancy. In animal studies, artesunate has been associated with foetal toxicity during the first trimester of pregnancy. To date, clinical data regarding safety in the first trimester have not indicated an increased risk of foetal harm. Treatment with artesunate should not be withheld during the first trimester if it is potentially life-saving for the mother. As in other populations, the evidence that artesunate reduces the risk of death from severe malaria compared to other treatments should be borne in mind.

In a study of 461 pregnant Thai women (44 in their first trimester) who were treated with artemisinins (predominantly artesunate), there was no obvious evidence of adverse effects amongst the 414 women for whom pregnancy outcomes were known. The observed rates of abortion, stillbirth, congenital anomalies and low birth weight were comparable to community rates.

In clinical trials from 1999 to 2006, 2,045 pregnant women in Thailand, the Gambia, and Sudan were treated with artesunate, either alone or in combination with other antimalarials, including quinine, mefloquine, atovaquone-proguanil and sulfadoxine-pyrimethamine. In these patients, most of whom were in their second or third trimesters of pregnancy, there were no significant differences compared to the general community in birth weights, duration of gestations, placental weights, or rates of congenital abnormalities, or in growth and developmental parameters of infants monitored for one year.

Breastfeeding / lactation

Limited information indicates that dihydroartemisinin, the active metabolite of artesunate, is present at low levels in breast milk. The drug levels are not expected to cause any adverse effects in breastfed infants. The amount of drug present in breast milk does not protect the infant from malaria.

4.7 Effects on ability to drive and use machines:

There is no information on the effect of artesunate on the ability to drive or use machines. The patient's clinical status should be considered when assessing ability to drive or operate machinery.

4.8 Undesirable effects:

The most important reported side effect of artesunate is a rare severe allergic reaction (estimated risk approximately 1 in 3000 patients), which has involved urticarial rash as well as other symptoms, including hypotension, prutitus, oedema, and/or dyspnoea.

More common minor side effects associated with IV administration have included dizziness, light-headedness, rash, and taste alteration (metallic/ bitter taste). Nausea, vomiting, anorexia and diarrhea have also been reported, however it is uncertain whether such events have been symptoms of severe malaria.

Adverse events considered at least possibly related to artesunate are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (1/100–1/10), uncommon (1/1000–1/100), rare (1/10 000–1/1000), and very rare (< 1/10 000).

Blood and lymphatic systems disorders

Uncommon: Neutropenia and anaemia (both occasionally severe), thrombocytopenia

Very rare: Pure red cell aplasia

Frequency unknown: Post-treatment anaemia (see below), mild and transient decrease in reticulocyte count

Nervous system disorders

Common: Dizziness, light-headedness, headache, insomnia, tinnitus (with or without decrease in auditory function)

Very rare: Peripheral neuropathy (or paraesthesia)

Respiratory disorders

Common: Cough, nasal symptoms

Gastrointestinal disorders

Common: Altered taste, nausea, vomiting, abdominal pain or cramps, diarrhoea

Rare: Raised serum amylase, pancreatitis

Hepatobiliary disorders

Uncommon: Transient rises in liver transaminases (AST, ALT)

Rare: Hepatitis

Skin and subcutaneous tissue disorders
Common: Rash, alopecia
Musculoskeletal and connective tissue disorders
Common: Arthralgia, muscle disorders
General disorders and administration site conditions
Common: Fatigue, malaise, fever, pain at injection site
Immune system disorders
Uncommon: hypersensitivity
Post-treatment anaemia
In general, despite transient decreases in reticulocyte counts, clinically significant anaemia attributed to IV artesunate has not been common in clinical trials in severe malaria. However, in a case-series of 25 patients in Europe who were treated with IV artesunate for severe malaria acquired in an endemic area, 6 patients developed significant post-treatment haemolytic anaemia, presenting as late as 3 weeks after treatment, and 5 of them required transfusion. The aetiology of the haemolysis remains unknown.

4.9 Overdose:
Experience of acute overdose with artesunate is limited. A case of overdose has been documented in a 5-year-old child who was inadvertently administered rectal artesunate at a dose of 88 mg/kg/day over 4 days, representing a dose more than 7-fold higher than the highest recommended artesunate dose. The overdose was associated with pancytopenia, melena, seizures, multiorgan failure and death.
Treatment of overdose should consist of general supportive measures.

5. Pharmacological Properties
5.1 Pharmacodynamic Properties:
Pharmaco-therapeutic group: Antimalarial
ATC code: P01BE03

Mechanism of action
Artesunate is a hemisuccinate derivative of dihydroartemisinin, which is itself formed by the reduction of artemisinin. Artemisinin is a sesquiterpene lactone endoperoxide extracted from qinghao (sweet wormwood, Artemisia annua L.), a plant which has been used for centuries in traditional Chinese medicine.
The mechanism of action of the artemisinins likely involves cleavage of the internal endoperoxide bridge through reaction with haeme within the infected erythrocyte, thereby generating free radicals which alkylate vital parasite proteins. However, artemisinins have also been reported to inhibit an essential parasite calcium adenosine triphosphatase.
The artemisinins are distinguished from other antimalarials by their ability to kill all erythrocytic stages of the malaria parasite, including the relatively inactive ring stage and late schizonts, as well as the gametocytes responsible for malaria transmission. Artesunate and the artemisinins are the most rapid acting of the antimalarials, and they have also been shown to enhance splenic clearance of infected erythrocytes by reducing cytoadherence.
In vitro, dihydroartemisinin (DHA), the active metabolite of artesunate, exhibits similar potency against chloroquine-resistant and chloroquine-sensitive clones of P. falciparum.
Artesunate and the other artemisinins are essentially inactive against extra-erythrocytic forms, sporozoites, liver schizontes or merozoites.

Clinical efficacy and safety

In the SEAQUAMAT (South East Asian Quinine Artesunate Malaria Trial), an international randomised, open-label, multicenter trial conducted in Bangladesh, India, Indonesia and Myanmar, 1461 patients with severe malaria (including 1259 adults) were treated intravenously with either

artesunate or quinine. Artesunate was administered at 2.4 mg/kg IV at 0, 12 and 24 h and then every 24 h until the patient could tolerate oral medication. Quinine was given IV at 20 mg/kg over 4 hours, followed by 10 mg/kg over 2-8 hours, 3 times daily until oral therapy could be started. Mortality in the artesunate group was 15% versus 22% in the quinine group, for a reduction in risk of death of 34.7% (p=0.0002). Subgroup analysis suggested a greater benefit of artesunate versus quinine in patients with parisitemia >10%. The reduction in mortality observed in the 202 paediatric patients (<15 years of age) appeared consistent with the overall results, however the number of children was too small to demonstrate statistical significance. IV artesunate was well tolerated, while quinine was associated with a substantially increased risk of hypoglycaemia.

Paediatrics

The AQUAMAT (African Quinine Artesunate Malaria Trial) was an international, randomized open-label multicenter trial which sought to extend the results of the SEAQUAMAT study by comparing parenteral artesunate versus IV quinine for severe malaria in 5425 African children (< 15 years) in 9 African countries. Dosing was similar to SEAQUAMAT, except that both artesunate and quinine could be administered either intravenously or intramuscularly, using the same doses for IM and IV administration for each drug. Roughly one third of patients received study drug by intramuscular injection. Mortality in the artesunate group was 8.5% compared to 10.9% in the quinine group, resulting in a relative risk reduction for death of 22.5% (p=0.0022); the risk reduction was similar for IV and IM administration. In addition, although the risk of neurological sequelae in survivors in both groups did not differ significantly by 28 days following treatment, in-hospital coma, convulsions, and deterioration of coma were all less frequent in the artesunate-treated patients. As in the SEAQUAMAT, post-treatment hypoglycaemia was more common in the quinine-treated group.

5.2 Pharmacokinetic Properties:

Intravenous

After intravenous injection artesunate is very rapidly biotransformed to its active metabolite, dihydroartemisinin (DHA). Consequently, artesunate half-life (t½) is estimated to be less than 5 minutes. Following a single IV dose of 2.4 mg/kg, maximum artesunate plasma concentrations (Cmax) were estimated to be 77 μmol/L in a study in Gabonese children with severe malaria, and 42 and 36 μmol/L in two studies in Vietnamese adults with uncomplicated malaria.

High concentrations of DHA are observed within 5 minutes of artesunate IV administration. In the above studies (adult and paediatric), the ranges of values for the estimated time to maximum concentration (tmax) and t½ for DHA were 0.5-15 minutes and 21-64 minutes, respectively, while DHA Cmax values ranged from 5.3-10.6 μmol/L.

Intramuscular

Artesunate is rapidly absorbed following intramuscular injection, and peak plasma levels are generally achieved within 30 minutes of administration. Thus, after IM injection of 2.4 mg/kg of artesunate, absorption was rapid in Gabonese children and Vietnamese adults, with Tmax values of 8 and 12 minutes, respectively. The corresponding artesunate t1/2 values were

estimated to be 48 minutes in children and 41 minutes in adults, and Cmax values were 1.7 and 2.3μmol/L, for children and adults, respectively.
After IM injection artesunate Cmax values were therefore lower by roughly 45-fold in children and 20-fold in adults when compared to IV injection. However, rates of artesunate elimination in children and adults were 32-fold and 13-fold slower, respectively, following IM injection, compared to IV administration.

Distribution

DHA has been shown to substantially accumulate in *P. falciparum*-infected erythrocytes. Plasma protein binding of dihydroartemisinin was determined to be 93% in patients and 88% in healthy volunteers

Metabolism and elimination

Artesunate is extensively and rapidly hydrolysed by plasma esterases, with possible minimal contribution by CYP2A6. The main metabolite, dihydroartemisinin, accounts for most of the *in vivo* antimalarial activity of oral artesunate, however, following IV administration. artesunate may contribute more significantly. DHA is further metabolized in the liver via glucuronidation and is excreted in the urine; α-dihydroartemisinin-β-glucuronide has been identified as the major urinary product in patients with *falciparum* malaria.

Special population:

No pharmacokinetic data are available for patients with impaired renal or hepatic function. However, based on the known mechanisms of metabolism and elimination of artesunate, combined with clinical data from patients with severe malaria and accompanying renal and/or hepatic compromise of various degrees, no dose modifications are considered necessary in renal or hepatic impairment.

5.3 Preclinical safety data:

General toxicity

Artesunate presents low acute toxicity. After repeated administration of 50 mg/kg/day in rats and 82.5 mg/kg/day in dogs, i.e. approximately 10 and 17 times the proposed maximal therapeutic dose in man, evidence of toxicity was observed in the haematopoietic organs, the immune system and response, the liver and kidneys.

Genotoxicity

Artesunate did not show any mutagenic or clastogenic potential in *in vitro* and *in vivo* tests (Ames, mouse micronucleus).

Carcinogenesis

No studies of the carcinogenic potential of artesunate have been conducted.

Reproductive toxicology studies

Oral artesunate caused dose-dependent foetal toxicity in rats, rabbits and monkeys, resulting in foetal resorption and abortion, as well as a low incidence of cardiac and skeletal defects. The no-observed-adverse-effect-level (NOAEL) was 12 mg/kg in pregnant monkeys (3 and 7 day exposures) and the no or low adverse effects level was 5-7 mg/kg in pregnant rats or rabbits (12 day exposures), both of which are above the therapeutic dose range (2.4-4.8 mg/kg) and expected duration of exposure for treatment of severe malaria in humans. In rats, the embryo-fetuses were most sensitive from gestational days 9-14; at other times embryotoxicity was significantly reduced.

Safety pharmacology studies

A slight sedative effect, decrease in body temperature, mild natriuretic effect and a decrease in creatinine clearance were observed with artesunate after single intravenous doses of 200 mg/kg (mice), 450 mg/kg (rats, rabbits and dogs) and following single oral doses of 180

mg/kg in male rats. Beagle dogs administered IV artesunate at 10, 20, 50, and 50 mg/kg for 14 days did not display significant clinical effects, including any signs of neurotoxicity, effects on body weight, ECG abnormalities (including QT interval changes), heart rate, blood pressure, or respiratory rate.

6. Pharmaceutical particulars
6.1 List of Excipients:
Not Applicable

6.2 Incompatibilities:
Not Applicable

6.3 Shelf life:
24 Months

6.4 Special precautions for storage:
Store below 30°C. Keep medicines out of the reach of children.

6.5 Nature and contents of container:
5 ml Clear glass Vial.

6.6 Special precautions for disposal:
No special requirements.

7. DATE OF REVISION OF THE TEXT
----

8. NAME AND ADDRESS OF MANUFACTURER
PHARMAX (INDIA) PVT LTD
9 KURLA INDUSTRIAL ESTATE, OFF NARAYAN
NAGAR GHATKOPAR WSET
MUMBAI 400086, MAHARASHTRA STATE INDIA

ARTESUNATE FOR INJECTION (COMBIPACK) REBOK		
MODULE I :	**ADMINISTRATIVE PARTICULARS OF THE PRODUCT**	
Document	**1.3**	**Product Information**

(B) SODIUM BICARBONATE INJECTION BP 2 ML AMPOULE

1. Name of the medicinal product

1.2 (Invented) Name of the medicinal product
SODIUM BICARBONATE INJECTION BP

1.2 Strength
Composition:
Sodium Bicarbonate BP 5 % W/V
Water for Injection BP Q.S.
Bicarbonate and Sodium Concentrate 595 Millimoles/Litre Each

1.3 Pharmaceutical Form
Injection

2. Qualitative and Quantitative Formula
Batch Size: 85 Lit.

Sr. No.	Name of Ingredient	Quantity/ Vial (mg)	Quantity/Batch (Kg)	Functions
1.	Sodium Bicarbonate BP	5% W/V	0.41	Active
2.	Disodium Edetate BP	0.07 mg	0.07	Stabilizer
3.	Water for Injection BP	Q.S.	Q.S. to 85 Lit.	Vehicle

3. Pharmaceutical form
Clear Colourless Liquid.

4. Clinical particulars
4.1 Therapeutic Indication:
Sodium Bicarbonate Injection is indicated in adults and children for:
• Correction of metabolic acidosis associated with cardiac arrest in patients with pre-existing metabolic acidosis
• Cardiac arrest associated with hyperkalaemia with pre-existing metabolic acidosis
• Life threatening hyperkalaemia with pre-existing metabolic acidosis
• Tricyclic antidepressant overdose.
Sodium bicarbonate should only be used after other resuscitative measures such as cardiac compression, ventilation, adrenaline and antiarrhythmic agents have been attempted.
In neonates, Sodium Bicarbonate is indicated for:
• Correction of metabolic acidosis associated with cardiac arrest in patients with preexisting metabolic acidosis
• Cardiac arrest associated with hyperkalaemia with pre-existing metabolic acidosis
• Life threatening hyperkalaemia with pre-existing metabolic acidosis
No benefits have been demonstrated from the routine use of sodium bicarbonate in resuscitation of neonates. In neonates, sodium bicarbonate is recommended in resuscitation only in cases of prolonged cardiac arrest, irresponsive to other therapy, after establishment of adequate ventilation and circulation.

4.2 Posology and method of administration:

Posology

The posology depends largely on the extent of the acid-base imbalance. This should be checked regularly.

Adults: The usual dose is 1mmol/kg (1ml/kg 8.4% solution) followed by 0.5 mmol/kg (0.5 ml/kg 8.4% solution) given at 10-minute intervals.

Paediatric population: The usual dose is 1mmol/kg by slow IV injection. (1 ml/kg 8.4% solution) In premature infants and neonates, the 8.4% solution should be diluted 1:1 with 5% dextrose.

Elderly: As for adults.

Method of administration

For intravenous administration only.

4.3 Contraindications:

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
• Conditions where sodium intake is restricted (e.g. renal failure, hypertension, oedema, congestive heart failure)
• Patients with hypoventilation (risk of worsening of acidosis)
• Metabolic or respiratory alkalosis
• Patients with a history of urinary calculi
• Patients with coexistent potassium depletion or chloride depletion, hypocalcaemia and hypernatraemia.

4.4 Special warnings and precautions for use:

Whenever sodium bicarbonate is used intravenously, arterial blood gas analyses, in particular arterial/venous blood pH and carbon dioxide levels, should be performed before and during the course of treatment to minimise the possibility of overdosage and resultant alkalosis.

Accidental extravascular injection of hypertonic solutions may cause vascular irritation or sloughing. The use of scalp veins should be avoided.

Whenever respiratory acidosis is concomitant with metabolic acidosis, both pulmonary ventilation and perfusion must be adequately supported to get rid of excess CO_2.

Administration of sodium bicarbonate to a patient with inadequate minute ventilation can cause worsening of the acidosis.

The treatment of metabolic acidosis must, if possible, be combined with concurrent treatment to combat the primary cause of the acidosis, for example the administration of insulin in uncomplicated diabetes, or blood volume restoration in shock.

In long-term therapy, care is essential to prevent the risk of overdose and alkalosis. Therefore, repeat administrations of fractional doses, or an infusion, should be given while regularly monitoring the acid-base balance and electrolytes. As soon as the most severe symptoms are under control, the dose and frequency of administration must be reduced until normal values have been restored.

There is no evidence to support the use of bicarbonate therapy in the treatment of hypoperfusion-induced lactic academia associated with sepsis.

SODIUM BICARBONATE INJECTION BP contains sodium

This medicinal product contains 23.00 mg sodium per ml, equivalent to 1.15% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction:
Caution should be used when administering sodium ions to patients receiving corticosteroids or corticotrophin.
Urinary alkalisation will increase the renal clearance of medicinal products which are acid in nature e.g. tetracyclines, especially doxycycline, acetylsalicylic acid, chlorpropamide, lithium, methenamine. It increases the half life and duration of action of basic drugs such as quinidine, amphetamines, ephedrine, pseudoephedrine, memantine and flecainide. Sodium bicarbonate is known to increase renal tubular reabsorbtion of mecamylamine causing hypotention.
Hypochloraemic alkalosis may occur if sodium bicarbonate is used in conjunction with potassium depleting diuretics such as bumetamide, ethacrynic acid, frusemide and thiazides.
Concurrent use in patients taking potassium supplements may reduce serum potassium concentration by promoting an intracellular ion shift.

4.6 Fertility, Pregnancy and lactation:
Safe use in pregnancy has not been established. The use of any drug in pregnant or lactating women requires that the expected benefit be carefully weighed against the possible risk to the mother and child.
Patients requiring i.v. sodium bicarbonate are unlikely to be fit enough to breast feed.

4.7 Effects on ability to drive and use machines:
Not applicable; this preparation is intended for use only in emergencies.

4.8 Undesirable effects:
Metabolism and nutrition disorders:
Alkalosis, hypokalaemia, hypernatremia, hyperosmolarity, hypocalcemia, hypoglycemia, paradoxical intracellular acidosis.
Cardiac disorder:
Deterioration of hemodynamic status associated with volume overload.
Nervous system disorders:
Intracranial haemorrhage (in neonates), hyperirritability or tetany.
General disorders and administration site conditions:
Extravasation.
Incorrect administration (intra-arterial, paravenous) may cause tissue necrosis.

4.9 Overdose:
Symptoms: metabolic alkalosis accompanied by compensatory hyperventilation, paradoxical acidosis of the cerebrospinal fluid, severe hypokalaemia, hyperirritability and tetany.
Treatment: discontinue the administration of sodium bicarbonate, rebreathe expired air or, if more severe administer calcium gluconate especially if tetany is present. In severe alkalosis, an infusion of 2.14% ammonium chloride is recommended, except in patients with pre-existing hepatic disease. If hypokalaemia is present administer potassium chloride.

5. Pharmacological Properties
5.1 Pharmacodynamic Properties:
ATC Code: B05XA02
Sodium bicarbonate therapy increases plasma bicarbonate, buffers excess hydrogen ion concentration, raises blood pH and reverses clinical manifestations of metabolic acidosis.

5.2 Pharmacokinetic Properties:
Sodium bicarbonate is eliminated principally in the urine and effectively alkalises it.

5.3 Preclinical safety data:
Not applicable since sodium bicarbonate has been used in clinical practice for many years and its effects in man are well known.

6. Pharmaceutical particulars
6.1 List of Excipients:
Disodium Edetate BP
Water for Injection BP

6.2 Incompatibilities:
Not Applicable

6.3 Shelf life:
36 Months

6.4 Special precautions for storage:
Store below 30°C. Keep medicines out of the reach of children.

6.5 Nature and contents of container:
1 ampoule of 2 ml glass vial Sodium Bicarbonate Injection.

6.6 Special precautions for disposal:
No special requirements.

ARTESUNATE FOR INJECTION (COMBIPACK) REBOK		
MODULE I :	**ADMINISTRATIVE PARTICULARS OF THE PRODUCT**	
Document	**1.3**	**Product Information**

(C) SODIUM CHLORIDE INJECTION BP (0.9 % W/V)

1. Name of the medicinal product

1.3 (Invented) Name of the medicinal product
SODIUM CHLORIDE INJECTION BP (0.9 % W/V)

1.2 Strength
Composition:
Sodium Chloride BP 0.9 % W/V
Water for Injection BP Q.S.

1.3 Pharmaceutical Form
Injection

2. Qualitative and Quantitative Formula
Batch Size: 425 Lit.

Sr. No.	Name of Ingredient	Quantity/ Vial (mg)	Quantity/Batch (Kg)	Functions
1.	Sodium Chloride BP	0.9 % w/v	0.38	Active
2.	Water for Injection BP	Q.S.	Q.S. to 425 Lit.	Vehicle

3. Pharmaceutical form
Clear Colourless Liquid filled in Polyethylene Ampoules.

4. Clinical particulars
4.1 Therapeutic Indication:
For use in prophylactic and replacement therapy, requiring the use of isotonic saline solution.
In the reconstitution, dilution and making up of certain drugs.
As a saline irrigant.
As a priming fluid for haemodialysis procedures and to initiate and terminate blood transfusions.

4.2 Posology and method of administration:
In the prophylaxis or replacement therapy of extracellular fluid deficits, the dosage of sodium chloride injection BP 0.9% is dependent on the age, weight, clinical status and degree of deficiency, and must be determined on the individual basis.

4.3 Contraindications:
There are no absolute contraindications to use of Sodium Chloride Injection BP 0.9% w/v.

4.4 Special warnings and precautions for use:
Sodium Chloride Injection BP 0.9% w/v, should be administered with caution to patients with congestive cardiac failure, pre-eclampsia, impaired renal function or oedema with sodium retention. Care is also required with administering this solution to very young or to elderly patients. Pseudohyponatraemia is a condition in which spuriously low concentrations

of sodium are found when plasma sodium is measured by conventional methods. It may occur when there is an abnormally high concentration of large molecules and hence an abnormally low percentage of plasma water. This may occur in hyperlipaemia and hyperproteinaemia and has also been reported in patients with diabetes mellitus. Correct values may be obtained by referring the concentration to plasma water.
Before use, ensure that the container is undamaged and the contents clear in appearance. After use, discard any remaining solution.

4.5 Interaction with other medicinal products and other forms of interaction:
Concomitant administration of other sodium salts, may contribute to the sodium load. Only use as a pharmaceutical diluent where indicated in the manufacturer's literature.

4.6 Fertility, Pregnancy and lactation:
The solution is physiological saline and may be used during pregnancy and lactation.

4.7 Effects on ability to drive and use machines:
None known.

4.8 Undesirable effects:
Injudicious intravenous saline therapy (e.g. post-operative and in patients with impaired cardiac or renal function) may cause hypernatraemia. Osmotically induced water shift decreases intracellular volume, resulting in dehydration of internal organs, especially the brain, which may lead to thrombosis and haemorrhage. General adverse effects of sodium chloride excess in the body include: nausea, vomiting, diarrhoea, abdominal cramps, thirst, reduced salivary and lachrymal secretions, sweating, fever, hypotension, tachycardia, renal failure, peripheral and pulmonary oedema, respiratory arrest, headache, dizziness, restlessness, irritability, weakness, muscular twitching and rigidity, convulsions, coma and death. Excess chloride in the body may cause a loss of bicarbonate, with an acidifying effect. With judicious use of intravenous saline therapy these side effects can be avoided. If administered sub-cutaneously, any addition to the isotonic solution could render it hypertonic and cause pain at the site of injection.

4.9 Overdose:
Injudicious intravenous saline therapy (e.g. post-operatively or in patients with impaired cardiac or renal function) may cause hypernatraemia. Osmotically induced water shift decreases intracellular volume, resulting in dehydration of internal organs, especially the brain, which may lead to thrombosis and haemorrhage. General adverse effects of sodium chloride excess in the body include: nausea, vomiting, diarrhoea, abdominal cramps, thirst, reduced salivary and lachrymal secretions, sweating, fever, hypotension, tachycardia, renal failure, peripheral and pulmonary oedema, respiratory arrest, headache, dizziness, restlessness, irritability, weakness, muscular twitching and rigidity, convulsions, coma and death. Excess chloride in the body may cause a loss of bicarbonate, with an acidifying effect. With judicious use of intravenous saline therapy these side effects can be avoided.

5. Pharmacological Properties
5.1 Pharmacodynamic Properties:
The principal determinant of the effective osmolality of the extracellular fluids (and also of the intracellular fluids, since they remain in osmotic equilibrium with the extracellular fluids)

is the extracellular fluid sodium concentration. The reason for this is that sodium is the most abundant positive ion of the extracellular fluid. Negative ion concentrations of the body fluids are adjusted to equal those of the positive ions by renal acid-base control mechanisms. Furthermore, glucose and urea, the most abundant of the non-ionic osmolar solutes in extracellular fluids, normally only represent about 3% of the total osmolality. Therefore, in effect, the extracellular fluid sodium ion concentration controls over 90% of the effective osmotic pressure of the extracellular fluid. Sodium Chloride remains the most important single salt for prophylaxis or replacement therapy of deficits of extracellular fluid. Volume contraction, whether isotonic, hypotonic or hypertonic, may seriously impair the circulation (cardiac output falls and microcirculation is compromised) and prompt infusion of isotonic sodium chloride solution is indicated.

5.2 Pharmacokinetic Properties:
The homeostatic mechanisms involved in maintaining constant ion concentrations are well described in standard text books of physiology and biochemistry and are not, therefore, included here.

5.3 Preclinical safety data:
No further information other than that which is included in the Summary of Product Characteristics.

6. Pharmaceutical particulars
6.1 List of Excipients:
Water for Injection BP

6.2 Incompatibilities:
Not Applicable

6.3 Shelf life:
36 Months

6.4 Special precautions for storage:
Store below 30°C. Keep medicines out of the reach of children.

6.5 Nature and contents of container:
1 ampoule of 5 ml FFS of Sodium Chloride Injection (0.9 % W/V).

6.6 Special precautions for disposal:
No special requirements.
