1.3.1

Summary of Product Characteristics (SmPC)

1. Name of the medicinal Product

1.1 Name of the medicinal Product

Combipack of Artesunate for Injection, Sodium Bicarbonate Injection BP 5.0 % w/v & Sodium Chloride Injection 0.9 % w/v

1.2 Strength

Each Combipack Contains:

(A) One Vial of Artesunate for Injection

Each Vial Contains:

Artesunate (Sterile) 60 mg

(B) One Ampoule of 1 ml Sodium Bicarbonate Injection BP 5.0% w/v

(C)One Ampoule of 5 ml Sodium Chloride Injection BP 0.9% w/v

2. Qualitative and Quantitative Composition

2.1 Qualitative declaration

Artesunate

2.2 Quantitative declaration

1. Artesunate for Injection

Sr. No.	Ingredients	Specifications	Quantity (mg/vial)	Rational
Active Material				
1	Artesunate	In-House	60.00	Antimalarial Agent

2. Sodium Bicarbonate Injection BP 5.0 % w/v

Sr. No.	Ingredients	Specifications	Label Claim (% w/v)	Function
1	Sodium Bicarbonate	BP	5.000	Alkalizing agent
2	Water for Injections	BP	Q.S.	Vehicle

3. Sodium Chloride Injection BP 0.9 % w/v

Sr. No.	Ingredients	Specifications	Label Claim (% w/v)	Function
1	Sodium chloride	BP	0.900	Tonicity agent

2	Water for Injections	BP	Q.S.	Vehicle

3. Pharmaceutical Form

Dry Powder Injection

White to off white colour powder filled in 7.5 ml transparent glass vial

4. Clinical Particulars

4.1 Therapeutic Indications

Artesunate for Injection 60 mg is indicated for the treatment of severe malaria caused by Plasmodium falciparum, in adults and children.

4.2 Posology and Method of Administration

Adults and children: Artesunate injection is administered at a dose of 2.4 mg of Artesunate/kg body weight, by intravenous (I.V.) or intramuscular (I.M.) injection, at 0, 12 and 24 hours, then once daily until oral treatment can be substituted.

Administration:

The powder for injection is difficult to dissolve and care should be taken to ensure that it is completely dissolved before parenteral administration.

The formulation should be used immediately after reconstitution.

If the solution is cloudy or precipitate is present, the parenteral solution should be discarded.

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

The powder for injection should be reconstituted with 1 ml of sodium bicarbonate 5% w/v, shake vigorously till the solution become clear.

For I.V. Use: Add 5 ml of sodium chloride 0.9% w/v and mix again to prepare final concentration of 10 mg/ml for I.V. use. The required amount of drug for I.V. use should be administered slowly over a period of 2-3 minutes.

For I.M. Use: Add 2 ml of sodium chloride 0.9% w/v and mix again to prepare final concentration of 20 mg/ml for I.M. use.

4.3 Contraindications

It is contraindicated in patients with hypersensitivity to artesunate or other artemisinin derivatives.

4.4 Special Warnings and Special 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.

In cerebral malaria and complicated malaria, general supporting therapy is usually required.

Renal/hepatic impairment: Dose adjustment is not necessary in patients with hepatic or renal impairment.

Pregnancy: 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.

Lactation: The active metabolite of artesunate is excreted 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

4.5 Interaction with other medicinal products and other forms of interaction

Few clinical drug-drug interaction studies have been performed; however no clinically significant interactions have been identified.

4.6 Fertility, Pregnancy and Lactation

Pregnancy: 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.

Lactation: The active metabolite of artesunate is excreted 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

Not stated

4.8 Undesirable Effects

Blood and lymphatic systems disorders: Neutropenia and anaemia (both occasionally severe), thrombocytopenia, pure red cell aplasia, post-treatment anaemia, mild and transient decrease in reticulocyte count.

Nervous system disorders: Dizziness, light-headedness, headache, insomnia, tinnitus, peripheral neuropathy.

Respiratory disorders: Cough, nasal symptoms

Gastrointestinal disorders: Altered taste, nausea, vomiting, abdominal pain or cramps, diarrhoea, raised serum amylase, pancreatitis.

Hepatobiliary disorders: Transient rises in liver transaminases (AST, ALT), hepatitis.

Skin and subcutaneous tissue disorders: Rash, alopecia.

Musculoskeletal and connective tissue disorders: Arthralgia, muscle disorders

General disorders and administration site conditions: Fatigue, malaise, fever, pain at injection site.

Immune system disorders: Hypersensitivity.

4.9 Overdose

Experience of acute overdose with artesunate is limited. The overdose of artesunate is associated with pancytopenia, melena, seizures, multiorgan failure and death. Treatment of overdose should consist of general supportive measures.

5. Pharmacological Properties

5.1 Pharmacodynamics Properties

Artesunate is a hemisuccinate derivative of dihydroartemisinin, which is itself formed by the reduction of artemisinin. 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.

5.2 Pharmacokinetic Properties

Absorption: 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. Artesunate is rapidly absorbed following intramuscular injection, and peak plasma levels are generally achieved within 30 minutes of administration.

Distribution: Dihydroartemisinin (DHA) has been shown to substantially accumulate in P. falciparum infected erythrocytes. Plasma protein binding of dihydroartemisinin is determined to be 93% in patients and 88% in healthy volunteers.

Metabolism 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 IV administration. 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.

5.3 Preclinical Safety Data

Not applicable.

6. Pharmaceutical Particulars

6.1 List of Excipients

Sodium Bicarbonate BP

Sodium Chloride 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. Protect from light.

6.5 Nature and Contents of Container

5 ml clear glass USP type-III vial having 20 mm grey butyl rubber stopper & 20 mm blue F/O seal. Such one vial is packed in a "Lincoln" printed blister pack with 1 ml sodium bicarbonate injection & 5 ml sodium chloride injection, such one blister is packed in a printed carton with packaging insert.

6.6 Special precaution for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Registrant (Marketing Authorization Holder And Manufacturing Site Addresses)

7.1 Name and Address of Marketing Authorization Holder

GRACE JOHNSONS LTD.
446, OLD OJO ROAD, SATELLITE TOWN,
LAGOS, NIGERIA.

7.2 Name and Address of manufacturing site(s)

AARGE HEALTHCRAFT,
PLOT NO. 12A/1, SECTOR-2,
PARWANOO, DIST-SOLAN
HIMACHAL PRADESH (173220),
INDIA.

7.3 Marketing Authorization Number

To be included after obtaining first registration.

7.4 Date of First <Registration> / Renewal of The <Registration>

It will be applicable after registration of this product.

8. Date of Revision of the Text

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9. Dosimetry (If Applicable)

Not Applicable

10. Instructions for preparation of radiopharmaceuticals (if Applicable)

Not Applicable