SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

ARTECOSPE ®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each artesunate tablet contains 50 mg artesunate, each sulfadoxine/pyrimethamine tablet contains 500 mg sulfadoxine and 25 mg pyrimethamine. Each artesunate tablet contains 15 mg of sucrose. Each sulfadoxine/pyrimethamine tablet contains 20 mg of lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

The artesunate 50 mg tablets are white round tablets debossed with “AS” on one side and a score line on the other side.

The sulfadoxine/pyrimethamine tablets (500/25 mg) are white, round, and debossed with “SP” on both sides, with a score line on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

ARTECOSPE® (artesunate + sulfadoxine/pyrimethamine) is indicated for the treatment of uncomplicated cases of malaria due to Plasmodium falciparum strains which are susceptible to artesunate as well as to sulfadoxine /pyrimethamine.

The most recent official guidelines on the appropriate use of antimalarial agents and local information on the prevalence of resistance to antimalarial drugs must be taken into consideration for deciding on the appropriateness of therapy with artesunate tablets and sulfadoxine/pyrimethamine tablets. Official guidance will normally include WHO (http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf?ua=1&ua=1) and public health authorities’ guidelines (see also sections 4.4 and 5.1).

Artesunate + sulfadoxine/pyrimethamine should not be used in regions where resistance to any component is widespread.

This product is intended for use in children. Nonetheless, safety information is provided with respect to adult health issues such as liver disease, pregnancy and lactation, to allow full access to all relevant information.

4.2 Posology and method of administration

Tablets for oral administration.
A target dose of 4 mg/kg/day artesunate (AS) is given once a day for 3 days, with a single administration of 25/1.25 mg/kg sulfadoxine/pyrimethamine (S/P) on day 1. Therapeutic dose range is between 2–10 mg/kg/day artesunate and 25–70/1.25–3.5 mg/kg sulfadoxine/pyrimethamine. See table below.

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Sulfadoxine / pyrimethamine given as a single dose only on day 1</th>
<th>Artesunate given daily for 3 days</th>
<th>Total no. of tablets for treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily dose (mg)</td>
<td>Daily tablets</td>
<td>Daily dose (mg)</td>
</tr>
<tr>
<td>5 to &lt; 10</td>
<td>250/12.5</td>
<td>Half 500/25mg tablet</td>
<td>25</td>
</tr>
<tr>
<td>10 to &lt; 25</td>
<td>500/25</td>
<td>One 500/25mg tablet</td>
<td>50</td>
</tr>
<tr>
<td>25 to &lt; 50</td>
<td>1000/50</td>
<td>Two 500/25mg tablets</td>
<td>100</td>
</tr>
</tbody>
</table>

The tablets should be swallowed whole. Artesunate + sulfadoxine/pyrimethamine tablets should not be taken with a high-fat meal (see section 5.1).

Should vomiting occur within half an hour after dosing, a repeated dose should be taken. In case of further vomiting, treatment for severe malaria should be considered.

If a dose is missed it should be taken as soon as it is noted. The next dose should be taken after the prescribed interval. No double dose should be taken to make up for a forgotten tablet. It should be ensured that all doses of this regimen are administered.

### 4.3 Contraindications

Artesunate + sulfadoxine/pyrimethamine tablets are contraindicated in:

- Hypersensitivity to the active substances or to any of the excipients (see 6.1)
- Patients with sulfonamide allergy or intolerance.
- Pregnancy at term
- Infants less than 2 months old
- Patients with megaloblastic anaemia.
- Patients with severe impairment of liver or kidney function.

### 4.4 Special warnings and precautions for use

Hypersensitivity reactions

Treatment with artesunate + sulfadoxine/pyrimethamine should be stopped in any patient developing a rash or urticarial reaction because of the risk of severe allergic reactions. (See section 4.3.) Hypersensitivity to sulfadoxine may also cause interstitial nephritis, lumbar pain, haematuria and oliguria.
Treatment with sulfadoxine-pyrimethamine-containing products such as ARTECOSPE® should not be given to HIV-infected patients or other patients receiving cotrimoxazole (trimethoprim plus sulfamethoxazole) prophylaxis or treatment.

Artesunate + sulfadoxine/pyrimethamine has not been evaluated for the treatment of complicated malaria and is therefore not recommended.

Artesunate + sulfadoxine/pyrimethamine has not been evaluated in the treatment of malaria due to *Plasmodium vivax, Plasmodium malariae, Plasmodium ovale* or *Plasmodium knowlesi* and is therefore not recommended.

During mixed falciparum/vivax malaria epidemics, artesunate + sulfadoxine/pyrimethamine should not be used, as sulfadoxine/pyrimethamine is not effective against *P. vivax* in many places.

There is no evidence to support the use of artesunate + sulfadoxine/pyrimethamine for prevention of malaria.

Artesunate + sulfadoxine/pyrimethamine has not been studied specifically in patients with thalassaemia, sickle cell anaemia or G6PD-deficiency.

**Important information about some of the other ingredients**
The artesunate tablet contains sucrose, the sulfadoxine/pyrimethamine tablet lactose.
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sacurase-isomaltase insufficiency may experience intolerance symptoms when taking this medicine.

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

Use of artesunate + sulfadoxine/pyrimethamine tablets in conjunction with trimethoprim or trimethoprim-sulfonamide or other sulfonamides or combinations thereof can result in an increased antifolate effect and corresponding haematologic side effects, and should be avoided.

### 4.6 Pregnancy and lactation

Women of childbearing potential treated with ARTECOSPE® should be advised to practise contraception during treatment and for three months after the last dose.

**Pregnancy**
There are no or a very limited amount of data from the use of artesunate + sulfadoxine/pyrimethamine in pregnant patients.
Studies in animals have shown reproductive toxicity of pyrimethamine, one of the active substances in ARTECOSPE® (see section 5.3).
ARTSCOSPE should only be used during pregnancy, especially in the first trimester, when the benefit is considered to outweigh the potential risks, and alternative first-line drugs are not available.
ARTECOSPE® should not be used in pregnancy at term.
If ARTECOSPE® is used for treatment during pregnancy, the co-administration of high dose folate supplementation (5 mg daily) should be avoided as this compromises the efficacy of ARTECOSPE® in pregnancy. Lower folate dosing (0.4–0.5 mg/day) should be used in women receiving artesunate + sulfadoxine/pyrimethamine for the treatment of malaria, or other treatments should be used.

**Lactation**
Antimalarials are excreted in human milk, but at therapeutic doses of ARTECOSPE® no effects on the breastfed newborns/infants are anticipated. ARTECOSPE® can be used during breast-feeding.

4.7 Effects on the ability to drive and use machines

Patients receiving artesunate + sulfadoxine/pyrimethamine tablets should be warned that dizziness may occur, in which case they should not drive or use machines.

4.8 Undesirable effects

Artesunate:
The adverse events for artesunate are listed below by body system, organ class and absolute frequency. They are not based on adequately sized randomized controlled trials, but on published literature data generated mostly during post-approval use. Since frequency estimates are highly variable across the studies, no frequencies are given for these events. When frequency estimates are available they are defined as follows: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (≤1/10,000). For some of these events, it is unclear whether they are related to artesunate or occur as a result of the underlying disease process.

Blood and lymphatic disorders
Uncommon: Neutropenia, low reticulocyte count, anaemia.

Cardiac disorders
Common: Mild electrocardiogram (ECG) changes (QTc and PR increase), atrial extrasystoles, non-specific T- wave changes.
Uncommon: Bradycardia
Not known: AV-block, possible QT-prolongation.

Gastrointestinal disorders
Very common: Gastrointestinal disturbances (nausea, vomiting, abdominal pain, diarrhoea).

Hepato-biliary disorders
Uncommon: Elevated liver enzymes.

Neurological Disorders
Very common: Dizziness
Not known: Tinnitus, convulsions.

Skin disorders:
Not known: Rash, urticaria.

General disorders
Rare: Hypersensitivity (allergic) reactions.

Sulfadoxine/Pyrimethamine:
All major reactions to sulfonamides and pyrimethamine are reported below, even though they may not have been reported with the combination sulfadoxine/pyrimethamine.
Sulfadoxine shares the adverse effect profile of other sulfonamides, allergic reactions can be severe because of its slow elimination.

Blood and Lymphatic Disorders
Agranulocytosis, aplastic anaemia, megaloblastic anaemia, thrombocytopenia, leukopenia, haemolytic anaemia, purpura, hypoprothrombinaemia, methemoglobinaemia, and eosinophilia.

Cardiac Disorders
Allergic myocarditis/pericarditis

Ear and labyrinth disorders
Tinnitus, vertigo

Endocrine Disorders
The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycaemic agents. Diuresis and hypoglycaemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents

Eye disorders
Periorbital edema, conjunctival and scleral injection, photosensitization,

Gastrointestinal Reactions
Glossitis, stomatitis, nausea, emesis, abdominal pains, diarrhea, feeling of fullness.

General Disorders
Drug fever, chills, periarteritis nodosa and LE phenomenon have occurred.

Hepatobiliary Disorders
Hepatitis, hepatocellular necrosis, pancreatitis, transient rise of liver enzymes.

Immune System Disorders
Hypersensitivity reactions, serum sickness, anaphylactoid reactions.

Musculoskeletal and Connective Tissue Disorders
Arthralgia.

Nervous System Disorders
Headache, peripheral neuritis, convulsions, ataxia, hallucinations, insomnia, fatigue, muscle weakness, polyneuritis.

Psychiatric Disorders
Mental depression, nervousness, apathy.

Renal and Urinary Disorders
Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria.

Respiratory Disorders
Pulmonary infiltrates resembling eosinophilic or allergic alveolitis.

Skin and Subcutaneous Tissue Disorders
Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, toxic epidermal necrolysis, urticaria, pruritus, exfoliative dermatitis, slight hair loss, Lyell's syndrome.
4.9 Overdose

**Symptoms:** Headache, anorexia, nausea, vomiting, agitation, convulsions, haematologic changes (megaloblastic anaemia, leucopenia, thrombocytopenia), glossitis, crystalluria.

**Treatment:** After acute intoxication, activated charcoal and adequate fluid administration; for convulsions, parenteral benzodiazepines, phenytoin or a barbiturate. Liver and renal function should be monitored and blood counts checked repeatedly for up to four weeks after the overdose. Should the blood dyscrasias referred to above occur, folinic acid (leucovorin) may be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaceutical group: Antimalarial
Artesunate ATC code: P01BE03
Pyrimethamine combinations ATC code: P01BD51

**Artesunate**

Artesunate is a hemisuccinate derivative of dihydroartemisinin, which is obtained by the reduction of artemisinin, a sesquiterpene lactone endoperoxide, extracted from a plant used in traditional Chinese medicine, known as sweet or annual wormwood (*Artemisia annua*).

The mechanism of action of artemesunate has been widely studied and appears well established. The artemesunate endoperoxide bridge is split by haeme within the infected erythrocyte, generating singlet oxygen. Parasite proteins, particularly in membranous structures, are thus alkylated, leading to parasite death.

In-vitro experiments in *P. falciparum* have shown that artemisinin derivatives are active against a broad spectrum of the life cycle of the parasite, from the relatively inactive ring stage to late schizontes. The schizonticidal and gametocyticidal activities of artemesunate, administered orally have been demonstrated in vivo on chloroquine-sensitive strains of Plasmodium (*P. berghei* in mice and *P. knowlesi* in monkeys) and on chloroquine-resistant strains (*P. berghei* in mice).

In-vitro, artesunate appears to be inactive against extra-erythrocyte forms, sporozoites, liver schizontes or merozoites.

When administered orally, artesunate consistently acts more quickly than orally administered chloroquine and intravenous quinine in all animal models studied, regardless of the strain or dose tested. In macaques (the animal model most similar to humans) infected with a chloroquine-resistant strain of *P. knowlesi*, cure was obtained with the same dose of artesunate and quinine.

Limited clinical data with the innovator and other artesunate-containing products do not indicate a relevant difference in the efficacy and safety profile of the drug, when the tablets are crushed in patients unable to swallow the tablets whole.

**Sulfadoxine**

Sulfadoxine is a slowly eliminated sulfonamide. Sulfonamides are structural analogues and competitive antagonists of p-aminobenzoic acid. They are competitive inhibitors of dihydropteroate synthase, the bacterial enzyme responsible for the incorporation of p-aminobenzoic acid in the synthesis of folic acid.

**Pyrimethamine**
Pyrimethamine is a diaminopyrimidine. It exerts its antimalarial activity by inhibiting plasmodial dihydrofolate reductase thus indirectly blocking the synthesis of nucleic acids in the malaria parasite. It is a slow-acting blood schizontocide and is also possibly active against pre-erythrocytic forms of the malaria parasite and inhibits sporozoite development in the mosquito vector. It has in vitro activity against the four long-established human malarias. There has been rapid emergence of clinical resistance.

5.2 Pharmacokinetic properties

Artesunate

Absorption and bioavailability
After oral administration artesunate is rapidly absorbed. Most of the artesunate is promptly biotransformed, mainly through plasma esterases, into the active metabolite dihydroartemisinin (DHA).

Following single dose artesunate 50 mg tablets administration in healthy volunteers, the mean (CV) artesunate Cmax value was 1.94 μg/ml, respectively and the corresponding value for AUC was 3.55 μg.h/ml. The median (range) artesunate tmax value was 33-85 min.

No pharmacokinetic data are available on crushing of tablets.

Distribution
DHA (dihydroartemisinin) has been shown to substantially accumulate in P. falciparum-infected erythrocytes. In man, artesunate is poorly protein bound.

Metabolism
Artesunate is extensively hydrolysed by plasma esterases and perhaps also by CYP2A6. Its main metabolite, DHA is presumed to account for most of the in vivo antimalarial activity. DHA is metabolised through glucuronidation.

Elimination
Artesunate has a plasma half-life of 3-29 minutes. The active metabolite DHA has a plasma half-life of 40 to 95 minutes.

Sulfadoxine/pyrimethamine

Absorption
Following single-dose administration of the pyrimethamine/sulfadoxine tablet in healthy volunteers (n=46), the mean (±SD) Cmax value for sulfadoxine was 183 (±18) μg/ml, and the corresponding value for AUC0-72h was 11037 (±1142) µg.h/ml. The median (range) sulfadoxine tmax value was 5.5 hours (4.0-48.0).

The mean (±SD) pyrimethamine Cmax value was 0.55 (±0.07) μg/ml, and the corresponding value for AUC was 29.8 (±3.4) μg.h/ml. The median (range) pyrimethamine tmax value was 5.5 hours (1.0-10.0).

Distribution
The volume of distribution for sulfadoxine and pyrimethamine is 0.14 L/kg and 2.3 L/kg, respectively. Plasma protein binding is about 90% for both sulfadoxine and pyrimethamine. Both sulfadoxine and pyrimethamine cross the placental barrier and pass into breast milk.

Metabolism
Pyrimethamine is transformed to several unidentified metabolites. About 5% of sulfadoxine appears in the plasma as acetylated metabolite, about 2 to 3% as the glucuronide.
Elimination
A relatively long elimination half-life is characteristic of both components. The mean values are about 100 hours for pyrimethamine and about 200 hours for sulfadoxine. Both pyrimethamine and sulfadoxine are eliminated mainly via the kidneys.

Characteristics in Patients
In malaria patients, single pharmacokinetic parameters may differ from those in healthy subjects, depending on the population concerned. In patients with renal insufficiency, delayed elimination of the components must be anticipated.

5.3 Preclinical safety data

Artesunate
- General toxicity:
  Artesunate’s toxicity appears in rat and dog after repeated oral administration of doses $\geq 50$ and 82.5mg/kg/day, respectively, i.e. 12.5 and 20.6 times the proposed therapeutic dose in man. In both species, toxicity is expressed as bone marrow changes (hypoplasia in both myeloid and erythroid populations with some regeneration at lower doses as expressed by increases in reticulocytes which then decrease at the severely toxic doses), liver and renal lesions (rat only) in addition to lymphoid hypoplasia in the dog only (decrease in circulating lymphocytes).

- Genotoxicity:
  In vitro tests (Ames test) and in vivo tests (micronucleus in mice) did not show any mutagenic potential.

- Carcinogenesis:
  No studies of the carcinogenic potential of artesunate have been conducted.

- Toxicity to reproduction:
  Embryofetal development studies in rats and rabbits showed a low incidence of cardiovascular malformation and syndrome of skeletal defects at doses close to embryolethal doses. The no or low adverse effect levels were in the range of 5 to 7 mg/kg/day. In these same studies the compound showed evidence of embryotoxicity from the dose of 6 mg/kg/day.

- Safety pharmacology studies
  Artesunate depresses all the major body functions (gastrointestinal, respiratory and cardiovascular systems) at very high doses in rat and cat, i.e. generally after intravenous administration of doses exceeding 300 mg/kg, which is the equivalent of about 75 times the recommended clinical dose administered orally. Renal function appears to be affected at relatively lower doses (from 12 mg/kg followed by infusion of 0.024 mg/min for one hour in the rat).

Sulfadoxine/pyrimethamine
- Genotoxicity:
  Pyrimethamine was not found mutagenic in the Ames test.

- Carcinogenesis:
  Pyrimethamine was not found carcinogenic in female mice or in male and female rats. Pyrimethamine was found to be mutagenic in laboratory animals and also in human bone marrow following 3 or 4 consecutive daily doses totaling 200 mg to 300 mg.

Toxicity to reproduction
Testicular changes have been observed in rats treated with 105 mg/kg/day of sulfadoxine/pyrimethamine and with 15 mg/kg/day of pyrimethamine alone. Fertility of male rats and the ability of male or female rats to mate were not adversely affected at dosages of up to 210 mg/kg/day of sulfadoxine/pyrimethamine. The pregnancy rate of female rats was not affected following their
treatment with 10.5 mg/kg/day, but was significantly reduced at dosages of 31.5 mg/kg/day or higher. Sulfadoxine-pyrimethamine has been shown to be teratogenic in rats when given in weekly doses approximately 12 times the normal human dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Artesunate 50mg Tablets
- Corn starch
- Dextrin
- Magnesium stearate
- Microcrystalline cellulose
- Sodium starch glycolate
- Sucrose

Sulfadoxine/Pyrimetamine 500mg/25mg Tablets
- Corn starch
- Hydroxypropyl cellulose
- Hydroxypropyl methylcellulose
- Lactose
- Magnesium stearate
- Microcrystalline cellulose
- Sodium lauryl sulfate
- Sodium starch glycolate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container

Primary packaging:
The primary packs are blister cards (composed of colourless and transparent PVC blisters sealed with an aluminium foil lid).

5 to < 25kg: Blister of 3 Artesunate (50mg) Tablets and 1 Sulfadoxine/Pyrimetamine (500mg/25mg) Tablet.

25 to < 50kg: Blister of 6 Artesunate (50mg) Tablets and 2 Sulfadoxine/Pyrimetamine (500mg/25mg) Tablets
Secondary packaging: Small box, middle box, and carton. Each small box contains one blister card, each middle box contains 25 small boxes; each carton contains 40 middle boxes.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER
Guilin Pharmaceutical Co. Ltd
No 43, Qilidian Road,
Guilin, Guangxi
People’s Republic of China 541004
Phone: 86-773-3841973
Fax: 86-773-3841973
http://www.guilinpharma.com

8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)
MA066

9. DATE OF PREQUALIFICATION
24 May 2012

10. DATE OF REVISION OF THE TEXT
May 2016

References
General:
Guidelines for the Treatment of Malaria, World Health Organization, Third edition
(http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf?ua=1&ua=1)

World Health Organization
WHOPAR, with part 4 Summary of Product Characteristics (SmPC) for Artesunate tablets
http://apps.who.int/prequal/WHOPAR/WHOPARPRODUCTS/WHOPAR_MA044.htm


Dosing recommendations:

Crushing of tablets:
Ashley EA et al. Tropical Medicine & International Health 2006;11(11):1653-60.

Drug interactions:
Artesunate 50mg Tablets +
Sulfadoxine/Pyrimethamine 500mg/25mg,
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German P et al, Clin Inf Dis 2007;44:889-90

**Drug-Food Effect**

**Undesirable effects:**
White NJ, Lancet Inf Dis 2007; Aug 7(8):549-58

**Overdose**
ACEP Clinical Policies Committee
Clinical policy: Critical issues in the evaluation and management of adult patients presenting to the emergency department with seizures.

Meirkord H et al, EFNS guideline on the management of status epileptic in adults