LUTHERMIN, ARTEMETHER INJECTION
SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities (term to be revised).
The medicine may be authorized for additional or different uses by national medicines regulatory authorities.

1. NAME OF THE MEDICINAL PRODUCT

LUTHERMIN Artemether Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains: Artemether injection 80mg

3. PHARMACEUTICAL FORM

Artemether is a lipid soluble methylether of Dihydroartemisinin Artemisinin is a novel sesquiterpene lactone, extracted from the leaves of the shrub Artemnesia annua and possesses an endoperoxidebridge which is a rare feature in natural products. The Endoperoxide Bridge is essential for its artimalarial activity. It has very rapid schizontocidal activity against blood forms of P. falciparum and P. vivax. After intramuscular administration, peak plasma concentrations are attained within about 6 hours. Artemether has been reported to clear fever in severe falciparum malaria within 30-84 hours.

Its **chemical formula** is 3R 5aS,6R, 8aS 9R. 105.12R. 12aR -Decahydro-10-methoxy-3,6,9-trimethy 3.12-0 312-epoxy-12H-pyrano(4.3-111 2-benzodioxepin Its molecular formula is CHOs, and its molecular weight is 298.4

Group: anti- malarial agent Oily solution for injection 80 mg in 1-ml ampoule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LUTHERMIN ARTEMETHER INJECTION,80mg, dosage form is indicated in as a potent and quick acting artimalarial agent, used for treating chloroquine resistant falciparium malaria, including cerebral malaria in adults, neonates, infants, children, adolescents aged Consideration should be given to official treatment guidelines for malaria (e.g. by WHO).

4.2 Posology and method of administration

Adults and children weighing 20 kg or more:

LUTHERMIN ARTEMETHER INJECTION is administered at a dose of :

Adult: dose 80mg twice a day one day 1 by intravenous (IV)or intramuscular (IM) injection
Followed by 80mg once a day for 4 days, max dose 480mg

Children weighing less than 20 kg:

LUTHERMIN ARTEMETHER INJECTION is administered at a dose of 1.6mg/ kg twice a day, followed by same dose once daily for 5 days, max dose is 9.6mg/ kg; a 3 day regime is also used alternately (see section 5.1).

Method of administration

Dosage and duration

– Child and adult:

3.2 mg/kg by IM injection on the first day followed by 1.6 mg/kg once daily

Weight	80 mg ampoule	
	Loading dose	maintenance dose
3-4 kg	0.2 ml	0.1 ml
5-6 kg	0.3 ml	0.15 ml
7-9 kg	0.4 ml	0.2 ml
10-14 kg	0.6 ml	0.3 ml
15-19 kg	0.8 ml	0.4 ml
20-29 kg	1.2 ml	0.6 ml
30-39 kg	1.6 ml	0.8 ml
40-49 kg	2 ml	1 ml
50-59 kg	2.5 ml	1.2 ml

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Treat parenterally for at least 24 hours (2 doses), then, if the patient can tolerate the oral route, change to a complete 3-day course of an artemisinin-based combination. If not, continue parenteral treatment once daily until the patient can change to oral route (without exceeding 7 days of parenteral treatment).

4.3 Contraindications

LUTHERMIN ARTEMETHER INJECTION is contraindicated in patients with hypersensitivity to Artemether or other artemisinins orto any of the components of the formulation listed in section 6.1.

The following conditions are contraindicated with this drug.

Conditions:

- low amount of magnesium in the blood.
- low amount of potassium in the blood.
- torsades de pointes, a type of abnormal heart rhythm.
- Slow heartbeat.
- Prolonged QT interval on EKG.
- Abnormal EKG with QT changes from birth.

4.4 Special warnings and precautions for use

Non-falciparum malaria

Artemether has not been evaluated in the treatment of severe malaria due to *Plasmodium vivax, Plasmodiummalariae* or *Plasmodium ovale.*

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 LUTHERMIN ARTEMETHER INJECTION. Relevant treatment guidelines should be consulted such as those of the WHO and public health authorities (see reference sectionat end of this SmPC).

Post-treatment haemolytic anaemia
Delayed haemolytic anaemia following treatment with injectable artemether has been observed in children inmalaria endemic areas and in non-immune travelers presenting with severe falciparum malaria. The risk wasmost pronounced in patients with hyperparasitaemia and in younger children. Some cases have been severe and required blood transfusion. Vigilance for delayed onset anaemia is therefore advised, particularly in hyperparasitaemic patients and younger children, and prolonged follow-up should be considered (e.g. 14-28 days). As the overall benefit-risk ratio remains highly favourable for injectable Artemether in the treatment of severe malaria, WHO strongly recommends its continued use, refer to relevant treatment guidelines (see reference section at end of this document).

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 Artemether, 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 Artemether have been similar in adult and paediatric populations.

Warnings and precautions *for* **Artemether***? ... Caution should be exercised in patients with history of liver or kidney disease, heart*

Excipients

This medicinal product contains Camellia Oil

4.5 Interaction with other medicinal products and other forms of interaction

Artemether 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 minutes) and the potential for drug-drug interactions appears limited. *In vitro* drug-interaction studies have demonstrated minimal effects of Artemether on cytochrome P450 isoenzymes. Few clinical drug-drug interaction studies have been performed. An increase in plasma concentrations of artemether was observed with nevirapine and a reduced plasma concentration of dihydroartemisinin was observed when artemether isgiven with ritanovir.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Severe malaria is especially hazardous during pregnancy, therefore this drug **should not be used during the first trimester of pregnancy unless there are no alternatives**; this drug should be considered

during the second and third trimesters of pregnancy only if the benefit to the mother outweighs the risk to the fetus.

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In animal studies, Artemether has been associated with fetal toxicity during the first trimester of pregnancy.Limited clinical experience with the use of Artemether in the first trimester of pregnancy as well as clinicaldata from more than 4,000 pregnant women, treated with artemisinin derivatives in the second and third trimester, do not indicate adverse effects of Artemether on pregnancy or on the health of the fetus/newborn child.

Breastfeeding

Limited information indicates that Dihydroartemisinin, the active metabolite of Artemether, 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.

Fertility

No specific studies with Artemether in humans have been conducted to evaluate effects on fertility. In a reproduction toxicity study in rats, testicular and epididymal lesions were seen, but there were no effects on fertility (see section 5.3). The relevance of this finding for humans is unknown.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most important reported side effect of Artemether is a rare severe allergic reaction (estimated risk approximately 1 in 3000 patients), which has involved urticarial rash as well as other symptoms, includinghypotension, pruritus, 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 havealso been reported, however it is uncertain whether such events have been symptoms of severe malaria.

Adverse events considered at least possibly related to Artemether are listed below by body system, organ classand 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 haemolyticanaemia,*, mild and transient decrease in reticulocytecount

Nervous system disorders

Common: Dizziness, light-headedness, headache, insomnia, tinnitus (with or without decrease inauditory 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, pancreatitisHepatobiliary disorders

Adverse effects Neurotoxicity has been observed in animal studies but not in humans. Cardiotoxicity has been observed following administration of high doses of artemether*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*

Cases of delayed haemolytic anaemia have been identified in non-immune travelers following treatment of severe malaria with injectable Artemether. Some were severe and required blood transfusions. In a study in African children aged 6 months to 10 years of age in malaria endemic areas, 5 out of 72 children (7%) experienced delayed haemolytic anaemia following treatment with injectable artesunate, and one child required transfusion. Risk was increased with hyperparasitaemia in all age groups and with younger age in children. Onset of haemolysis and anaemia was evident by 14-28 days after Artemether treatment. Vigilancefor this adverse event is advised.

Paediatric population:

The safety profile of injectable Artemether is similar in children and adults.

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are askedto report any suspected adverse reactions to the marketing authorization holder, or, if available, via the national reporting system.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimalaria, ATC code: P01BE03

In the body, Artemether is metabolized into the active metabolite metabolite dihydroartemisinin. The drug works against the erythrocytic stages of *P. falciparum* by inhibiting nucleic acid and protein synthesis. Artemether is administered in combination with lumefantrine for improved efficacy. Artemether has a rapid onset of action and is rapidly cleared from the body. It is thought that Artemether provides rapid symptomatic relief by reducing the number of malarial parasites. Lumefantrine has a much longer half life and is believed to clear residual parasites.

Mechanism of action

Artemether 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 alkylatevital parasite proteins. However, artemisinins have also been reported to inhibit an essential parasite calciumadenosine 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 gametocytesresponsible 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 byreducing cytoadherence.

In vitro, dihydroartemisinin (DHA), the active metabolite of artesunate, exhibits similar potency againstchloroquine-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 Artemether 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 Artemether or quinine.

Artemether 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 suggesteda greater benefit of artesunate versus quinine in patients with parasitaemia>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. Post-treatment hypoglycaemia was more common in the quinine-treated group.

Paediatrics

The AQUAMAT (African Quinine Artemether Malaria Trial) was an international, randomized open-label multicenter trial which sought to extend the results of the SEAQUAMAT study by comparing parenteral Artemether versus IV quinine for severe malaria in 5425 African children (< 15 years) in 9 African countries (Mozambique, The Gambia, Ghana, Kenya, Tanzania, Nigeria, Uganda, Rwanda, and Democratic Republic of the Congo). Dosing was similar to SEAQUAMAT, except that both Artemether and quinine could be administered either intravenously or intramuscularly, using the same doses for IM and IV administration foreach drug. Roughly one third of patients received study drug by intramuscular injection. Mortality in the Artemether group was 8.5% compared to 10.9% in the quinine group, resulting in a relative risk reduction fordeath 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 daysfollowing 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

Pharmacokinetics of Artemether

Absorption	
Oral bioavailability	Not applicable
Food effect	Not applicable
Distribution	
Volume of distribution (mean)	Not available

Plasma proteinbinding*in vitro*	Artemether and lumefantrine are both highly bound to human serum proteins in vitro (95.4% and 99.7%, respectively). Dihydroartemisinin is also bound to human serum proteins (47% to 76%).
Tissue distribution	Dihydroartemisinin accumulates substantially in *P.falciparum*-infected erythrocytes
Metabolism	
	Rapidly metablized to its active metabolite, dihydroartemisinin. **Hover over products below to view reaction partners** • Artemether ○ → Dihydroartemisinin (DHA) ○ → 9,10-dihydrodeoxy-artemsinin ○ → Alpha-dihydroartemisinin ○ → Deoxyartemsinin ○ → Deoxydihydro-artemisinin
Active metabolite(s)	Dihydroartemisinin is further metabolised through glucuronidation
Elimination	
Elimination half life	Artemether, 1.6 +/- 0.7 and 2.2 +/- 1.9 hr; Dihydroartemisinin, 1.6 +/- 0.6 and 2.2 +/- 1.5 hr
% of dose excreted in urine	NA*
% of dose excreted in faeces	NA*

*Information not available.

5.3 Preclinical safety data

General toxicity

Animal studies on acute toxicity show that the LD50 of Artemether in mice is a single i.g. administration of 895mg/kg and a single i.m. injection of 296mg/kg dose; in rats, the LD50 is a single i.m. injection of 597mg/kg dose.

Genotoxicity

Artemether did not show any mutagenic or clastogenic potential in *in vitro* and *in vivo* tests (Ames, mousemicronucleus).

Carcinogenesis

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

Reproductive toxicology studies

Artemether caused dose-dependent fetal toxicity in rats, rabbits and monkeys, resulting in fetal resorptionand 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. A study of artemether administered to male rats daily for 6 weeks noted testicular and epididymal lesions, although these lesions did not affect fertility. The lesions were reversible after cessation of treatment.

6. PHARMACEUTICAL PARTICULARS

List of excipients

Artemether injection: No excipients

Solvent: Camellia Oil

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months, at least 5/6th of the shelf life must remain at the time of shipment.
The supplier will provide manufacturer’s stability test data substantiating the claimed shelf life in the offered package

6.4 Special precautions for storage

Artemether Injection should be kept in a tightly closed container protected from light in a cool, dry place away from the reach of children

6.5 Nature and contents of container

Artemether injection is a sterile Clear, colourless or almost colourless oily solution. Artemether Injection contains Artemether.

Each ampoule shall contain 1 ml of Artemether Injection. Sufficient overages are added as per Pharmacopoeia so that 1 ml of extractable Volume can be achieved. The ampoule should be sufficiently transparent to permit visual inspection of the contents. 6 Ampoules are packed in thermo-formatted trays having high rigidity and sufficient impact strength to provide break resistance packaging

Each ml shall contain –Artemether 80 mg

Pack size: A small box containing six ampoules of Artemether injection and a leaflet showing the summary Instructions for the product

7. SUPPLIER

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