SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medical product

Comether

2. Qualitative and quantitative composition

Each tablet contains Artemether 20mg and Lumefantrine 120mg

3. Pharmaceutical Form

Film-coated tablets
Yellow film-coated tablets, with light yellow cores, engraved with "A+L"

4. Clinical Particulars

4.1 Therapeutic indications:

Comether™is a fixed combination of artemether and lumefantrine which acts as a blood schizontocide. It is indicated for:

Treatment of adults and children with infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*, Comether™is effective against both drug-sensitive and drug-resistant *P. falciparum.* it is also recommended for malaria infections acquired in areas where the parasites may be resistant to other antimalarials, well as "stand-by emergency treatment" for non-immune tourists and business travelers, will be able to obtain prompt medical attention if malaria is suspected.

4.2 Posology and method of administration

Dose may be taken with fluids. Patients should be encouraged to resume normal eating as soon as food can be tolerated since this improves absorption of artemether and lumefantrine.
In the event of vomiting within 1 hour of administration a repeat dose should be taken. Non-immune patients and for stand-by emergency treatment a 3-day course is recommended,

Treatment dosage in adults:
With four tablets as a single dose at the time of initial diagnosis, again after 8 hours and then twice daily on each of the following two days (total course comprises 24 tablets).

Treatment dosage in children:

BODY WEIGHT	**Day 1**		**Day 2**		**Day 3**	
	initial diagnosis	8 hour later	morning	evening	morning	evening
5-<15kg	1tablet	1tablet	1tablet	1tablet	1tablet	1tablet
15-<25kg	2tablets	2tablets	2tablets	2tablets	2tablets	2tablets
25-<35kg	3tablets	3tablets	3tablets	3tablets	3tablets	3tablets
≥35kg	4tablets	4tablets	4tablets	4tablets	4tablets	4tablets

Treatment dosage in elderly patients
Although no studies have been carried out in the elderly, no special precautions or dosage adjustments are considered necessary in such patients.

Treatment dosage in patients with renal or hepatic impairment

Although no specific studies have been carried out, no special precautions or dosage adjustments are considered necessary for these conditions.
Most patients with acute malaria present with some degree of related hepatic impairment. The adverse event profile did not differ in patients with and those without hepatic impairment. Moreover, baseline abnormalities in liver function tests improved in nearly all patients after treatment with Comether™**.**

New and recrudescent infections in adults and children
Data for a limited number of patients show that new and recrudescent infections can be treated with a second course of Comether™**.***In-vitro* studies involving samples from patients with recrudescent infection showed no significant decrease in the sensitivity of *P. falciparum* to either artemether or lumefantrine.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

4.4 Special warning and precautions

Comether™has not been evaluated for the treatment of complicated malaria. Few patients several antimalarials are known to cause QTc-prolongation and a slight QTc-prolongation without clinical symptoms has been observed in a treated with Comether™, mainly in cases where concomitant dehydration or electrolyte imbalance was present. No correlation was found between QTc-prolongation and peak plasma concentration in individual patients. Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.

4.5 Interaction with other medical products and other forms of interactions

No specific drug interaction studies in humans have been conducted with Comether™**.** However, no safety issue that could be attributed to drug interactions arose during clinical studies with Comether™, in which most patients received antipyretic medication, antibiotics and fluid and electrolyte replacement.

In-vitro studies with artemether at therapeutic concentrations revealed no significant interactions with cytochrome P450 enzymes.
Lumefantrine was found to inhibit CYP2D6 *in vitro*. This may be of clinical relevance for compounds with a low therapeutic index known to be metabolized by this enzyme (e.g. neuroleptics and tricyclic antidepressants).

The likelihood of adverse effects on the safety and efficacy of Comether™due to drug-drug interactions is minimal in view of its short duration of administration and wide therapeutic index.

4.6 Pregnancy and lactation

The safe use of artemether and lumefantrine during pregnancy has not been established.

Reproductive toxicity studies in rats and rabbits have shown no evidence of teratogenicity for the combination or for the individual components, lumefantrine and artemether.

Although artemisinins are known to be embryotoxic in animals Comether™was not embryotoxic in rats at doses of ≦25mg/kg. However, artemether alone showed materno-, feto- and embryo- toxicity at 10mg/kg in rats and 30mg/kg in rabbits.

Comether™ treatment should only be considered if the expected benefit to the mother outweighs the risk to the fetus.

4.7 Effects on ability to drive and use machines

Patients receiving Comether™ should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

4.8 Undesirable effects

The frequency of adverse experiences reported in clinical trials of Comether™ for the treatment of malaria was generally similar to or lower than that of other antimalarial drugs used in the clinical trials. Many of the adverse experiences observed during clinical testing are due to the disease rather than to Comether™, although some symptoms that are part of the normal clinical picture of acute malaria may be caused or exacerbated by Comether™**.**

The most common adverse experiences (≧1%) in patients treated with Comether™ for which causality is suspected are: Central nervous system: Sleep disorder, headache, dizziness; Cardiovascular system: Palpitation; Gastrointestinal tract: Abdominal pain, anorexia, diarrhoea, vomiting, nausea; Skin and appendages: Pruritus, rash; Respiratory tract: Cough; Musculoskeletal system:Arthralgia, myalgia; Others: Asthenia, fatigue; Comether™ did not affect haematological or clinical chemistry parameters.

4.9 Overdose

In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Blood schizontocide agent, the site of antiparasitic action of both components is the food vacuole of the malarial parasite, where they are thought to interfere with the conversion of haem, a toxic intermediate produced during haemoglobin breakdown, to the non-toxic haemozoin, malaria pigment. Lumefantrine is thought to interfere with the polymerisation process, while artemether generates reactive metabolites as a result of the interaction between its peroxide bridge and haem iron. Both artemether and lumefantrine have a secondary action involving inhibition of nucleic acid and protein synthesis within the malarial parasite, Data from *in-vitro* and *in-vivo* studies show that Comether™ does not induce resistance.

The independent antimalarial activity of both lumefantrine and artemether is enhanced by their combination into Comether™, which has been shown to potentiate the blood schizontocidal effects. It is also effective against drug-resistant strains of *P. falciparum* malaria. Comprehensive *in-vitro* studies using laboratory-maintained and fresh-field parasite isolates from different malaria endemic areas have shown marked synergy of the two components.

Results of comparative clinical trials indicate that Comether™ also clears gametocytes more rapidly than non-artemisinin antimalarials.

5.2 Pharmacokinetic properties

Pharmacokinetic characterisation of Comether™ is limited by the lack of an intravenous formulation, and the very high inter- and intrasubject variability of artemether and lumefantrine plasma concentrations and derived pharmacokinetic parameters (AUC, C_{max}).

Absorption
Artemether is absorbed fairly rapidly with peak plasma concentrations reached about 2 hours after dosing. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration about 6-8 hours after dosing. Food enhances the absorption of both artemether and lumefantrine: in healthy volunteers the relative bioavailability of artemether was increased more than two-fold, and that of lumefantrine sixteen-fold, compared with fasted conditions when Comether™was taken after a high-fat meal. Food has also been shown to increase the absorption of lumefantrine in patients with malaria, although to a lesser extent (approximately two-fold), most probably due to the lower fat content of the food ingested by acutely ill patients. The food interaction data indicate that absorption of lumefantrine under fasted conditions is very poor (assuming 100% absorption after a high-fat meal, the amount absorbed under fasted conditions would be<10 of the dose).Patients should therefore be encouraged to take the medication with a normal diet as soon as food can be tolerated.

Distribution
Artemether and lumefantrine are both highly bound to human serum proteins *in vitro* (97.9% and 99.9%, respectively). Comparable binding values were observed in animals.
Distribution has not been further investigated in humans, but in rats artemether is well distributed throughout the body, with some affinity for the brown fat and adrenal glands, while lumefantrine has an affinity for adipose and glandular tissue and to some extent for the lungs, spleen (due to slow elimination from lymphoid tissue) and bone marrow.

Metabolism
Artemether is rapidly and extensively metabolized (substantial first-pass metabolism) both *in vitro* and in humans. Human liver microsomes metabolize artemether to the biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the enzyme CYP3A4/5. This metabolite has also been detected in humans *in vivo*. lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. *In vivo* in dogs and rats, glucuronidation of lumefantrine takes place directly and after oxidative biotransformation. *In vitro* lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Elimination
Artemether is rapidly cleared from plasma with an elimination half-life of about 2 hours. Lumefantrine is eliminated very slowly with a terminal half-life of 2-3 days in healthy volunteers and 4-6 days in patients with falciparum malaria.

No urinary excretion data are available for humans. In rats and dogs unchanged artemether has not been detected in faeces and urine due to its rapid and high-first-pass metabolism, but several metabolites (unidentified) have been detected in both faeces and urine. Lumefantrine is eliminated via the bile in rats and dogs, with excretion primarily in the faeces. After oral dosing in rats and dogs qualitative and quantitative recovery of metabolites in bile and faeces was relatively low, most of the dose being recovered as parent drug.

5.3 Preclinical safety data
Mutagenicity
No evidence of Comether™mutagenicity was detected in *in vitro* or *in vivo* tests. In the micronucleus test myelotoxicity was seen at all dose levels (500, 1000 and 2000mg/kg), but recovery was almost complete 48 hours after dosing.

Carcinogenicity
Carcinogenicity studies with Comether™ were not conducted.

Reproductive toxicity studies
Reproductive toxicity studies with Comether™ in rats showed both materno-and embryotoxic effects at doses ≧100mg/kg but without evidence of teratogenicity at any level. These effects were also seen at doses>60mg/kg in a subsequent rat study. In rabbits materno- and embryotoxicity were seen at 175mg/kg but no fetotoxicity or teratogenicity found in the next lower dose treatment.
Lumefantrine doses as high as 1000mg/kg showed no evidence to suggest materno-, embryo- or fetotoxicity or teratogenicity in rats and rabbits. Artemether also showed no effects in rabbits at doses up to 25mg/kg, but at 30mg/kg materno-, embryo- and fetotoxicity were observed. In rats, however, materno-, feto- and embryotoxicity were all noted at 10mg/kg, but without evidence of teratogenicity at any dose level.

6. Pharmaceutical Particulars

6.1 List of excipients
Croscarmellose sodium
Silicon dioxide
Microcrystalline cellulose
Hypromellose
Magnesium Stearate
Polysorbate 80

6.2 Incompatibilities
Not applicable

6.3 Shelf life
36 months (3 years)

6.4 Special precautions for storage
Store below 30℃.
The preparation should not be used after the date marked “EXP” on the pack.

6.5 Nature and contents of containers
8 tablets per sheet, and 3 sheets in one small paper box

7. Marketing Authorization Holder

KPC Pharmaceuticals, Inc.
Business Address: No.166, Keyi Road, High and New Technology Development Zone, Kunming, Yunnan Province, P.R.China
Tel: +86-871-68311225
Fax: +86-871-68256814
E-mail: registry@kpc-cotec.com

8. Marking Authorization number
04683/07082/REN/2019

9. Date of First Authorization/Renewal of the Authorization
24-October-2019

10. Date of revision of the text
June 2023