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Evaluation of Bioequivalence and Cardio-Hepatic Safety of a Single Dose of Fixed Dose Combination of Artemether and Lumefantrine

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Abstract

Background and objective: The existing fixed-dose combination, Coartem® (artemether 20 mg and lumefantrine 80 mg) requires 4 tablets per dose and a total of 24 tablets for the six-dose regimen for the treatment of uncomplicated P. falciparum malaria compromising the patient compliance. Also, the cardiotoxicity due to lumefantrine because of its structural similarity with halofantrine remains a matter of debate in therapeutics.

To enhance the patient compliance, the fixed-dose combination of artemether/lumefantrine (80/480 mg) is formulated by Sequel Pharmachem Pvt. Ltd. India. In the present study, this fixed dose combination (test product) was evaluated for its bioequivalence to the reference product, Coartem® 20/120 mg (artemether 20 mg and lumefantrine 120 mg) of Novartis Pharma Ltd. with assessment of cardio-hepatic safety.

Methods: A randomized, open label, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study with comparative safety evaluation was conducted on 72 healthy Indian human subjects under a fed condition. Quantification of artemether, dihydroartemisinin, and lumefantrine was done by a validated LC-MS/MS method. For bioequivalence, AUC_{0-240}, AUC_{0-inf} and C_{max} for artemether and lumefantrine were considered. Safety assessment was done by monitoring vital signs, QTc interval, serum ALT and AST values before and after treatment. Max QTc, baseline-corrected QTc_{max}, AST and ALT values were considered for statistical comparison between the two treatments. Drug plasma concentrations estimated at identical time points with the ECG recordings were correlated with ECG parameters.

Results: The test product was bioequivalent to the reference product as per the standard bioequivalence criteria. There was no clinically significant difference between the two treatments for all the safety parameters. No significant observation suggestive of cardiotoxicity and hepatotoxicity was noted in this study.

Conclusion: The test product can be used as a therapeutic option with likely better patient compliance in the treatment of uncomplicated P. falciparum malaria.

Introduction

An estimated 2.37 billion people live in areas at risk for transmission of P. falciparum malaria, primarily in sub-Saharan Africa, Central and South America, Southern Asia, and Papua New Guinea (Hay et al., 2009). A wide range of treatment options are available for the treatment of uncomplicated P. falciparum malaria. Drug resistance is a major impediment to the treatment of P. falciparum malaria. In the majority of regions where P. falciparum predominates, the parasites are resistant to common antimalarial drugs such as chloroquine and sulphadoxine/pyrimethamine (SP) (World Malaria Report, 2008).

The commonly used therapies such as quinine and mefloquine are associated with tolerability problems. Another alternative, atovaquone-proguanil, although apparently well tolerated, has not been well studied, and the results are not encouraging. Moreover, resistance to these more recent treatment options is emerging (Guidance for Industry, 2003). The six-dose regimen of artemether-lumefantrine is a good choice for treating acute and uncomplicated P. falciparum malaria because of its high efficacy, rapid resolution of clinical symptoms, and good tolerability. The safety, efficacy, and pharmacokinetics for the fixed-dose combination when given in a single dose of artemether 80 mg and lumefantrine 480 mg (4 tablets of Coartem®) in different regimes have been evaluated and proved in various clinical trials across the world involving hundreds of patients of acute and uncomplicated P. falciparum malaria. These were controlled comparative clinical trials involving a large number of patients of malaria. The safety and efficacy data obtained from all of these clinical trials conclude that artemether/lumefantrine combination in a single dose of 80/480 mg respectively is effective and safe in the treatment of malaria (Falade et al., 2008; Lefèvre et al., 2002). As per the recommendations, 4 tablets of the fixed-dose combination of artemether/lumefantrine (20/120 mg) should be given at 0hr and 8hrs on day 1 and morning and evening on days 2 and 3 in adults having body weight of more than 35 kg (Omari et al., 2005). Thus, the patient needs to consume a total of 24 tablets to complete the prescribed dose. Consumption of such a large number of tablets makes the "patient compliance" poor. In order to enhance the patient compliance, which is a critical step in improving the clinical outcome, a fixed-dose combination of artemether and lumefantrine

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(80/480 mg), maintaining the same ratio of 1:6 of artemether and lumefantrine is formulated. The rationale for designing such fixed-dose combination was to offer the equally efficacious alternative with an improved patient compliance in the treatment of uncomplicated P. falciparum malaria for adult patients with a body weight of more than 35 kg.

Due to the structural similarity between lumefantrine and halofantrine, lumefantrine is thought to produce cardiotoxicity similar to halofantrine. Cardiotoxicity in terms of QTc interval prolongation and arrhythmias always remained a matter of worry (Lefèvre et al., 2001). Drugs that prolong QT interval including antimalarials such as quinine and quinidine should be used cautiously following the artemether and lumefantrine combination due to the long elimination half-life of lumefantrine (3 to 6 days) and the potential for additive effects on the QT interval (Product monograph: Coartem® -artemether/lumefantrine, 2004).

As frequently seen in acute malaria, many patients show a certain degree of hepatic impairment as indicated by increased liver enzymes and/or hepatomegaly. Hence, it is desired that the antimalarial therapy instituted should not exaggerate the preexisting hepatic impairment if any (Cousin et al., 2008).

The present study was planned to evaluate the bioequivalence of the test product to the reference product so as to provide an equally effective treatment option with likely improved patient compliance. An assessment of cardiac and hepatic safety which is desired for the better therapeutic outcome in the treatment of uncomplicated P. falciparum malaria was also undertaken.

Objectives

Primary objective: To evaluate the bioequivalence of the test product (fixed-dose combination of artemether/lumefantrine 80/480 mg) of Sequel Pharmachem Pvt. Ltd. with 4 tablets of the reference product (Coartem® - artemether/lumefantrine 20/80 mg) of Novartis Pharma Ltd. in normal, healthy, adult male human subjects under non-fasting conditions in a randomized crossover study.

Secondary objective: To evaluate the cardiac and hepatic safety of a single dose of artemether 80 mg and lumefantrine 480 mg.

Subject and study design

This was a randomized, open label, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study with comparative safety evaluation in normal, healthy, adult, male human subjects under non-fasting conditions. The study was conducted as per the guidelines for conducting bioavailability/bioequivalence studies (Product monograph: Coartem® -artemether/lumefantrine, 2004).

The study was performed according to the Declaration of Helsinki for bio-medical research involving human subjects and the rules of Good Clinical Practices (ICH Harmonized Guideline for GCP, 1996).

The study protocol and other essential documents were approved by the local Independent Ethics Committee.

The compliance to the following inclusion and exclusion criteria was assessed by the investigator for each subject.

Inclusion criteria:

1. Male subjects in the range of 18 – 45 years of age and body weight within ± 15% of ideal weight (minimum 50 kg) as related to height and body frame according to Standard Life Insurance Corporation, India Chart.
2. Subjects with normal findings as determined by baseline history, physical examination and vital signs (blood pressure, pulse rate and body temperature).
3. Subjects with normal findings as determined by hematological tests, serum chemistry, serological tests, urine analysis, and 12 lead electrocardiogram.
4. Willingness to follow the protocol requirement as evidenced by written, informed consent.
5. Agreeing to, not using any medication (either prescribed, OTC or alternate medicines), including vitamins and minerals for 14 days prior to study and during the course of the study.
6. No history or presence of significant alcoholism or drug abuse in the past one year.
7. Non-smokers, non tobacco chewer

Exclusion criteria:

1. Requiring medication for any ailment including enzyme-modifying drugs in the previous 28 days, before first dosing day.
2. Any medical or surgical conditions, which might significantly interfere with the functioning of gastrointestinal tract, blood–forming organs etc.
3. History of cardiovascular, renal, hepatic, ophthalmic, pulmonary, neurological, metabolic, psychiatric diseases or any malignancy.
4. Subjects with history of recent myocardial infarction, cardiac arrhythmias, cardiac failure and convulsions.
5. Participation in a clinical drug study or bioequivalence study 90 days prior to present study.
6. Refusal to abstain from smoking or consumption of tobacco products until last sample collection of each period.
7. Use of xanthine-containing beverages or food, and grape fruit juice for 48.00 hours prior to each drug dose.
8. Blood donation 90 days prior to the commencement of the study.
9. History of problem in swallowing tablets or capsules.
10. Known history of hypersensitivity to Artemether or Lumefantrine or related drugs.

A total of 72 normal healthy adult subjects having mean weight 60.18 ± 8.32 kg, height 165.90 ± 5.51 cm and age 29.94 ± 6.41 years were included in the study.

This sample size was thought to be adequate for comparing the pharmacokinetic and safety parameters between the two treatments with required statistical power. The washout period of 47 days (more than ten half lives of the study drugs) was thought to be adequate to ensure complete elimination of the drugs from the body prior to the next study period. Any significant diseases or clinically significant abnormal findings were ruled out during the screening by obtaining complete medical history, performing complete physical examination, and laboratory investigations including haematology, biochemistry, serology, and urine analysis.

Methodology

The methodology was divided into clinical and analytical phases.

Clinical phase

After an overnight fast of at least 10 hours, the subjects were provided with a standard high fat high calorie breakfast as per USFDA

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guidelines 30 minutes prior to drug administration in each study period. The high fat high calorie breakfast yielded 927 kcal of which 529 kcal, 268 kcal and 124 kcal were derived from fat, carbohydrate and protein respectively.

The subjects were administered either of the treatments as per the randomization code with approximately 240 mL water in each study period. Being an open label study, the identity of the two treatments was not masked and the subjects were informed about the type of treatment (test or reference) before the drug administration in each study period.

A total of 27 blood samples (6 mL each) were collected in vacutainers containing heparin at 00.00 (pre-dose), 00.50, 01.00, 01.50, 02.00, 02.50, 03.00, 03.50, 04.00, 05.00, 05.50, 06.00, 06.50, 07.00, 07.50, 08.00, 08.50, 09.00, 10.00, 12.00, 16.00, 24.00, 48.00, 96.00, 144.00, 192.00, and 240.00 hours post-dose within 2 minutes of scheduled sampling time. To obtain plasma, the vacutainers were centrifuged at 3500 RPM for 10 minutes at 5°C ± 3°C. The plasma samples were stored in deep freezer maintained at -20°C ± 5°C.

The supervising medical officers or nursing staff under the supervision of principal investigator measured and monitored the vital signs. Clinical examination was done before check-in, before check-out, and during the last sample collection in each study period. Vital signs (blood pressure, pulse rate, respiratory rate and oral temperature) were measured at 00.00 (pre-dose), 01.00, 03.00, 06.00, 12.00, 24.00, 48.00, 96.00, 144.00, 192.00 and 240.00 hours post dose during each study period. The subjects were monitored for adverse events and complaints if any throughout the course of the study.

Twelve-lead ECGs were recorded during screening, at pre-dose, at 1.00, 2.00, 3.00, 4.00, 8.00, 12.00, and 24.00 hrs post-dose and on completion of the study or on discontinuation of the subject from the study. The QT intervals obtained from the ECG recordings done prior to dosing (pre-dose) and repeatedly thereafter were studied during each period. The rate-corrected QT interval (QTc) was calculated by using Bazett's equation as QTc = QT interval in second/√RR interval in second. The following ECG parameters were calculated:

1) $QTc_{baseline}$: The value of QTc obtained from pre-dose ECG recording.
2) Max QTc: The maximum QTc interval observed during the period of 24 hrs post-dose.
3) Baseline-corrected QTc_{max}: The difference between Max QTc and $QTc_{baseline}$.

These values were calculated for each subject treatment wise. The mean and standard deviation (SD) were calculated and considered for statistical comparison.

Estimation of serum aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT) were done to assess the hepatic functions before and 24hrs after the treatment during both study periods. These values were calculated for each subject treatment wise. The mean and standard deviation were calculated and considered for statistical comparison.

Bioanalytical phase

For each analyte, the analytical method validation included 0.5 ml of human plasma samples and solid-phase extraction process. The detection was done by LC-MS/MS method.

Artemether and dihydroartemisisnin: Metaxalone was used as an internal standard. The lower limit of quantification was 2.000 ng/ml for artemether and 2.000 ng/ml for dihydroartemisinin. The linearity range was 2.000 - 250.000 ng/ml for artemether and 1.990 - 248.750 ng/ml for dihydroartemisinin.

Lumefantrine: Glimepiride was used as an internal standard. The lower limit of quantification was 100.000 ng/ml. The linearity range was 100.000 - 20000.000 ng/ml.

The linearity range for each analyte was enough to quantify the expected concentration range from subject's plasma with the proposed dose of artemether and lumefantrine.

Statistical analysis

Pharmacokinetic evaluation: A non-compartmental method was used to calculate the pharmacokinetic parameters using drug concentration time profile. The data set for estimation of pharmacokinetic parameters was prepared using SAS® Software (Version 9.1.3). The estimation of pharmacokinetic parameters and their comparison was also carried out using the same software. T_{max} was evaluated by non-parametric Wilcoxon test procedure using SAS® Software (Version 9.1.3). Analysis of variance, equivalent to Schuirmann's two one-sided tests procedure, was performed on log-transformed parameters $C_{max,}$ AUC_{0-t} and AUC_{0-inf} including sequence, subjects nested within sequence, period, and treatment as factors. A probability value of 0.05 was selected as the level of significance. The randomization for this study was generated using the PROC PLAN program on statistical software SAS® 9.1.3.

Artemether and lumefantrine were considered for statistical analysis and establishing bioequivalence. The analysis of dihydroartemisinin was done for profiling purpose only. The 90% parametric confidence intervals were constructed for the ratios of the means of log-transformed C_{max}, AUC_{0-t} and AUC_{0-inf} for both the treatments. Bioequivalence was to be concluded if the 90% confidence intervals for C_{max}, AUC_{0-t}, and AUC_{0-inf} fell within the standard acceptance range of 80.00 – 125.00%.

Safety evaluation: For comparative safety evaluation, the pre-treatment and post-treatment ECG recordings, laboratory investigations (AST and ALT), and vital measurements were obtained. Max QTc and baseline-corrected QTc_{max} were calculated for each subject. The mean values were compared between the treatments to find the difference. The change in the mean AST and ALT values from baseline (pre-dose) for both the treatments were calculated and compared.

Results

Pharmacokinetic evaluation

A total of 72 healthy human adult subjects were enrolled in the study. A total of 64 subjects who completed the clinical phase of the study successfully were considered to draw statistical conclusions. The time required to achieve maximum plasma concentration (T_{max}) for artemether was 2.51 ±1.01 hr for test product and 2.49 ± 0.88 hr for the reference product. The T_{max} for dihydroartemisinin was 2.76 ± 0.95 hr for test product and 2.76 ± 0.95 hr for the reference product. Similar values for lumefantrine were 6.27 ± 1.65 hr and 5.98 ± 1.00 hr for the test and reference products respectively.

It was observed that the ratios for Geometric Least Square Means and 90% Confidence Intervals were within the acceptance criteria of 80% to 125% for $C_{max,}$ $AUC_{0-t,}$ and AUC_{0-inf} for artemether and lumefantrine (Table 1).

There was no significant sequence effect for log transformed C_{max}, AUC_{0-t} and AUC_{0-inf} for artemether and lumefantrine. Period

Drug	*Parameters*	Geometric mean		% Ratio	90% Confidence Interval for Log-transformed data	
		Test (A)	Reference (B)	A/B	Lower Limit	Upper Limit
Artemether	AUC_{0-inf}	290.27	264.66	109.68	102.82	116.99
	AUC_{0-t}	280.00	256.33	109.23	102.36	116.57
	C_{max}	95.15	86.84	109.57	100.99	118.87
Lumefantrine	AUC_{0-inf}	111398.22	117231.98	95.02	87.63	103.04
	AUC_{0-t}	100920.81	106366.51	94.88	87.27	103.16
	C_{max}	5469.22	5857.72	93.37	87.63	99.48

Table 1: Geometric Means and 90% Confidence Intervals (n=64) for artemether and lumefantrine.

Adverse Event	Test Product (A)	Reference Product(B)
Headache	02 (3.03%)	02 (2.86%)
Giddiness	-	01 (1.43%)
Vertigo	-	01 (1.43%)
Vomiting	-	02 (2.86%)
Diarrhoea	-	01 (1.43%)
Nausea	-	01 (1.43%)
Cough	-	01 (1.43%)
Sinus Bradycardia	01 (1.51%)	-
Hypoglycemia	-	01 (1.43%)
Leucocytosis	02 (3.03%)	-
Total	**05 (7.58%)**	**10 (14.29%)**

Table 2: Incidence of Adverse Events in the Study.

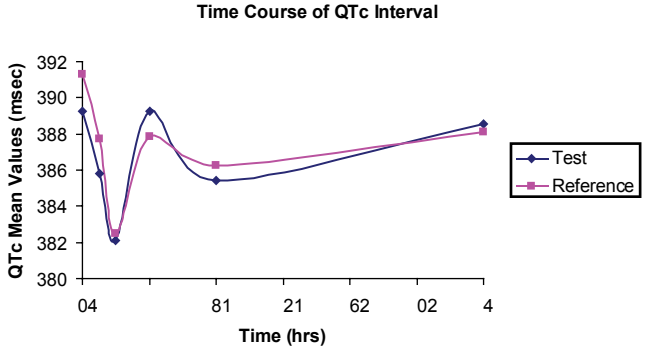

Figure 1: Time course of QTc interval during the study.

effect was found to be significant for log transformed $C_{max,}$ AUC_{0-t} and AUC_{0-inf} for artemether and lumefantrine. Since the environmental and procedural conditions were kept identical during both the study periods, this period effect can be ignored.

Significant treatment effect was found only for log-transformed AUC_{0-t} and AUC_{0-inf} for artemether. This effect might be present due to the difference in the formulation, but it does not seem to have any impact on study outcome as the confidence interval for the log transformed pharmacokinetic parameters fell in the acceptance range. Thus, the treatment effect can be ignored.

The subject within the sequence effect was found to be significant ($p<0.05$) for log-transformed C_{max}, AUC_{0-t} and AUC_{0-inf} for artemether and lumefantine. This statistical difference is not likely to have any clinical significance as it simply tells that subjects do differ from each other.

No pre-dose concentration of the study drugs was observed in period II thereby ruling out any carryover effect. This proved that the washout period was adequate for complete elimination of the study drugs from the body.

Safety evaluation

A total of 72 subjects were enrolled in the study of which 64 subjects completed the study as per the protocol. A total of 8 subjects were dropped out from the study as they did not report to the centre for period II due to personal reasons. Occurrence of adverse event was not the underlying cause for the discontinuation of any of these 8 subjects. As per the randomization code, a total of 66 and 70 subjects were exposed to the test and reference treatment respectively. A total of 15 adverse events were reported in the clinical phase of the study of which 05 events (7.58%) were observed in the test product treated subjects and 10 events (14.29%) were observed in the reference product treated subjects (Table 2). The adverse events were mild in severity. No serious adverse events were observed during both the periods of the study.

The safety analysis based on Max QTc and baseline-corrected QTc_{max} was performed. The results showed that there was no statistically significant difference (p value > 0.05) between the test and reference products for these parameters (Table 3). No clinically relevant differences in the QTc interval were observed in either of the treatments. Also, the drug plasma concentrations measured at identical time points of ECG recordings revealed no association with QTc interval abnormality.

The time course of QTc interval revealed absence of any significant increase or decrease in the QTc interval over a period of 24 hours post-dose during the clinical phase. The fluctuation in QTc interval was by a margin not greater than 10 msec in both the treatment groups. The time course of QT interval was characterized by initial small fall followed by normalization within 24 hours (Figure 1).

For each individual, the difference in serum AST and ALT values from the baseline was calculated for both the study treatments. The mean of these differences was calculated and considered for statistical comparison between two treatments. It had been observed that few subjects had relatively large difference in serum AST and ALT values from the baseline compared to others. However, none of the difference was clinically significant as the serum AST and ALT values were well within the acceptable limits. The dispersion (spread out) of such larger differences in few of these subjects around the mean difference has resulted in high standard deviation compared to their means (Table 4).

The change in mean AST and ALT values from the baseline (pre-study) was not statistically significant (p-value > 0.05) between the test and reference products. The levels of ALT were increased marginally from the baseline (as evident from the positive value of difference). On the contrary, the levels of AST were decreased marginally from the baseline (Table 4).

Discussion

A total of 72 adults, healthy, human male subjects were enrolled in the study. A total 64 subjects completed the clinical phase of the study successfully. Plasma samples of these 64 subjects were analyzed, and the data was considered for statistical evaluation. The ratios for geometric least square means and 90% confidence intervals were between the acceptance range of 80% to 125% for $C_{max,}$ $AUC_{0-t,}$ and AUC_{0-inf} for artemether and lumefantrine. Hence, the test product (fixed-dose combination of artemether 80 mg/lumefantrine 480 mg) of Sequel Pharmachem Pvt. Ltd. is bioequivalent to the reference

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Parameter	Treatment	Mean	SD	90% CI (A-B)		Difference	p value
				Lower	Upper		
Max QTc	Test (A)	406.11	13.03	-3.9638	3.2820	-0.34092	0.8757
	Reference (B)	406.58	11.86				
Baseline correctedQTc$_{max}$	Test (A)	16.83	14.67	-3.1362	5.9653	1.41452	0.6056
	Reference (B)	15.30	16.06				

Table 3: Statistical Analysis of QTc Interval.

Parameter	Treatment	Mean	SD	90 % CI (A-B)		Difference	p value
				Lower	Upper		
ALT- change from baseline	Test (A)	0.97	6.56	-0.1266	0.4979	0.1856	0.3247
	Reference (B)	0.94	6.35				
AST- change from baseline	Test (A)	-0.23	6.21	-0.2666	0.2757	0.0046	0.9776
	Reference (B)	-0.67	6.21				

Table 4: Statistical Analysis result of serum ALT and AST.

product (Coartem® - artemether/lumefantrine 20/80 mg) of Novartis Pharma Ltd. in terms of rate and extent of absorption under non-fasting condition.

The test and reference products were well tolerated. The percentage difference between the two treatments for occurrence of adverse events was insignificant. Except for sinus bradycardia observed in one subject, no other adverse event related to cardiovascular system was observed in the study. No adverse event suggestive of any hepato-billiary derangement was observed in any of the subjects. No serious adverse event was noted in the study. No clinically relevant differences in the QTc interval were observed in either of the treatments. All the ECG parameters remained well within the normal limits in both the treatments. No clinically significant trend or observation was noted. This observation is in accordance with the results observed by Lefèvre et al. (2002).

The plasma drug measurements revealed adequate systemic exposure to artemether, dihydroartemisinin, and lumefantrine well in line with the published data (Lefèvre et al., 2002; Product monograph: Coartem® -artemether/lumefantrine, 2004). If artemether and lumefantrine had any significant effects on cardiac conduction or repolarization, then there should have been a relationship between concentration and effect, but none was found in this study. No correlation between the length of the QTc interval and plasma drug concentrations was found for any of the compounds in our study. In fact, we observed that the QTc interval was decreased after dosing of both the study drugs. The fall in QTc interval was correlated with the T_{max} of artemether and dihydroartemisinin. In our opinion, the duration and the degree of fall in QTc interval was not enough to provoke any further investigation.

In one of the published studies conducted on healthy human subjects with multiple dosing of artemether and lumefantrine, the maximum mean change of 8 msec in the baseline corrected QTc interval was observed. Also, the change in QTc interval was dependent on the concentration of lumefantrine. A total of six doses of artemether and lumefantrine (80/480 mg per single dose) were given to the subjects in this study over a period of three days (Product monograph: Coartem® -artemether/lumefantrine, 2004). Considering the long half life of elimination for lumefantrine (4-5 days), the multiple dosing in such a short time might have resulted in increased plasma levels of lumefantrine due to cumulative effect. The increased levels of lumefantrine observed after the sixth dose of artemether and lumefantrine (80/480 mg) on third day of the therapy might have produced this small clinically insignificant increase in QTc interval.

We noted no elevation in serum AST and ALT levels in the present study for either of the treatments. Faye et al. (2007) titrated the levels of AST and ALT on day 0 and 14 in patients of malaria treated with artesunate/lumefantrine combination. In few patients, the rise in AST and ALT was observed but it was not significant clinically (not more than 2.5 × normal values). Our results are in accordance with the results noted by Faye et al. (2007).

Overall, the data generated in the present study provide strong evidence that the fixed dose combination of artemether 80 mg and lumefantrine 480 mg can be used safely and with anticipation of better patient compliance in the six-dose regimen for the treatment of uncomplicated P. falciparum malaria.

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