SCIENTIFIC DISCUSSION

This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

Name of the Finished Pharmaceutical Product:	Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets*
Manufacturer of the Prequalified Product:	Cipla Ltd. - India
Active Pharmaceutical Ingredients (APIs):	artesunate + mefloquine
Pharmaco-therapeutic group (ATC Code):	Artesunate, combinations (P01BF02)
Therapeutic indication:	Artesunate and Mefloquine (as hydrochloride) fixed dose combination tablets are indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum.*

* Trade names are not prequalified by WHO. This is under local drug regulatory authority's responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets is a fixed dose combination of 25 mg artesunate and 50 mg mefloquine (as hydrochloride). It is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum*, in the setting of either *P. falciparum* mono-infection or mixed infections.

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 a combination of mefloquine and artesunate. Official guidance will normally include WHO (http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf) and public health authorities' guidelines.

2. Assessment of Quality

Introduction

The assessment was done according to SOP 20 of the WHO Prequalification programme.

Active Pharmaceutical Ingredients (APIs)

Artesunate

Artesunate is manufactured in a two-step process from artemisinin via dihydroartemisinin (artenimol), followed by a purification step.

The API specifications are Ph.Int. based and include tests for description, solubility, identification (IR and HPLC), specific optical rotation, heavy metals, sulphated ash, water content (KF), pH, assay (HPLC), related substances (HPLC), residual solvents and particle size distribution.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packing material.

Mefloquine hydrochloride

Mefloquine hydrochloride API is described in the Ph.Int., Ph.Eur. and the USP.

Mefloquine contains two asymmetric carbons, thus two pairs of diastereomers are possible namely the (±) threo and (±) erythro forms. Mefloquine hydrochloride is manufactured as the (±) erythro compound, the pharmaceutical form, in several steps from the starting material for synthesis, 2-trifluoromethylaniline.

Mefloquine hydrochloride shows polymorphism and several forms have been reported. Form D is consistently produced, as demonstrated by XRPD on multiple batches.

The API specifications are pharmacopoeial based and include tests for appearance, solubility, melting point, identification (IR and chloride), appearance of solution, specific optical rotation, heavy metals, sulphated ash, water content (KF), assay (HPLC), related substances (HPLC), residual solvents and particle size distribution.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packing material.

Other ingredients

Other ingredients used in the core tablet formulation include croscarmellose sodium, magnesium stearate (vegetable grade) and microcrystalline cellulose. The commercially sourced proprietary film-coating mixture contains indigo carmine aluminium lake (FD & C Blue #2), hypromellose, macrogol, polysorbate 80 and titanium dioxide.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Each tablet contains 25 mg artesunate and 55 mg mefloquine hydrochloride equivalent to 50 mg mefloquine. The blue, round, smooth, biconvex, film-coated tablets are packaged in aluminium-aluminium blister strips.

The development of the final composition of the tablets has been described. The objective was to develop artesunate and mefloquine as a fixed-dose combination intended to be administrated orally as an immediate release tablet. Two strengths were developed: The higher strength (containing 100 mg artesunate and 220 mg mefloquine hydrochloride) has been developed as a first step, followed by the lower strength (containing 25 mg artesunate and 55 mg mefloquine hydrochloride) as a direct scale down thereof.

API-API and API-excipient compatibility studies have been conducted at stress conditions. It was concluded that artesunate is not stable under conditions of wet granulation. The process selected includes dry granulation (roller compaction) of mefloquine hydrochloride, with extra granular introduction of artesunate. The process development includes laboratory scale feasibility batches and scale up batches. Finally the tablets are film coated and packaged in aluminium-aluminium blisters to protect against moisture.

Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data on primary batches demonstrated the consistency of the process.

Specifications

The FPP specifications include tests for description, identification of the APIs and the colorants, water content, dissolution, assay (HPLC), related substances (HPLC), uniformity of dosage units (by content uniformity), residual solvent and microbiological examination of non-sterile products.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable under these storage conditions, with both APIs showing little to no degradation trend. The data support the proposed shelf-life and storage conditions as stated in the SmPC.

The posology in the Product Information describes the preparation of a suspension in water for administration to children who are unable to swallow tablets. The procedure described is supported by stability data.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Pharmacokinetics

To support the pharmacokinetics, the following studies have been submitted:

- Phase I study ASMQ-HNV (2005): a single dose study in 24 healthy subjects, comparing the pharmacokinetics of artesunate and mefloquine after administration of the 100/200 mg fixed dose combination tablet versus the individual reference formulations Lariam® and Arsumax®.

- Phase II study ASMQ-BKK: a multiple dose study in 50 patients diagnosed with malaria, comparing the pharmacokinetics of artesunate and mefloquine after administration of the 100/200 mg fixed dose combination tablet versus the individual reference formulations Lariam® and Arsumax®.

- Phase III study DND-ASM-07: a clinical study in patients diagnosed with malaria receiving the fixed dose combination tablet.

Assessment has been based upon own merits, as pharmacokinetics for this application are considered to support the pivotal clinical studies.

In studies ASMQ-HNV and ASMQ-BKK, validated high performance liquid chromatographic analytical methods have been applied to analyse for artesunate (AS), dihydroartemisinin (DHA) and mefloquine (MQ) in plasma. The calibration curve ranged from about 10 – 800 ng/ml for artesunate and dihydroartemisinin, and from about 25 – 1600 ng/ml for mefloquine.

In study DND-ASM-07, for the analysis of artesunate, dihydroartemisinin and mefloquine, validated analytical methods have been applied to analyse the analytes in plasma using LC-MS/MS. The calibration curve ranged from about 20 – 1500 ng/ml for artesunate, from about 40 – 3000 ng/ml for dihydroartemisinin, and from about 10 – 3500 ng/ml for mefloquine.

The objective of the **Phase I study ASMQ-HNV**, was to compare the bioavailability of the 100/200 mg artesunate/mefloquine fixed dose combination (test drug) with the same dose of the individual reference formulations (Arsumax®, Sanofi-Synthelabo, France and Lariam®, Roche, Switzerland). The comparison was performed as a single centre, open label, randomized, crossover study in healthy male subjects. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment Test:	- 2 tablets artesunate/mefloquine 100/200 mg (artesunate 200 mg + mefloquine 400 mg) Batch no. 070008 and 069002.
Treatment Reference:	- 4 tablets Arsumax® 50 mg (artesunate 200 mg) Batch no. 031201. - 2 tablets Lariam® 250 mg (mefloquine 500 mg) Batch no. B1100

A 90 day wash-out period was observed between administration of test and reference. Serial blood samples for analysis of artesunate and dihydroartemisinin were taken up to 24 h after administration and for mefloquine up to day 90 during each study period to obtain bioavailability characteristics.

The study was performed with 24 participants; data generated from a total of 24 subjects were utilized for analysis to establish pharmacokinetic parameters.

The pharmacokinetic variables for artesunate, dihydroartemisinin, total equivalent dihydroartemisinin (total DHA) and mefloquine are summarised in the following tables:

Artesunate

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD	Reference (R) arithmetic mean ± SD	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	0.6 ± 0.8	0.5 ± 0.3	-	-
C_{max} (ng/ml)	138 ± 56	206 ± 97	64.8	53.0 – 79.3
AUC_{0-t} (ng.h/ml)	125 ± 75	149 ± 71	76.7	61.5 – 95.7
AUC_{0-inf} (ng.h/ml)	182 ± 144	211 ± 72	-	-
T1/2 (h)	0.8 ± 0.8	0.5 ± 0.2	-	-

Dihydroartemisinin

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD	Reference (R) arithmetic mean ± SD	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	1.4 ± 0.8	1.1 ± 0.4	-	-
C_{max} (ng/ml)	694 ± 284	902 ± 351	74.8	59.1 – 94.6
AUC_{0-t} (ng.h/ml)	1712 ± 726	1963 ± 626	84.0	71.2 – 99.1
AUC_{0-inf} (ng.h/ml)	1958 ± 711	2058 ± 659	-	-
T1/2 (h)	1.8 ± 1.6	1.9 ± 1.1	-	-

Total equivalent Dihydroartemisinin*

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD	Reference (R) arithmetic mean ± SD	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	1.5 ± 0.8	0.9 ± 0.3	-	-
C_{max} (ng/ml)	733 ± 295	979 ± 363	72.7	57.7 – 91.6
AUC_{0-t} (ng.h/ml)	1798 ± 737	2068 ± 647	84.1	72.2 – 98.0
AUC_{0-inf} (ng.h/ml)	2048 ± 753	2138 ± 686	-	-
T1/2 (h)	1.9 ± 1.6	1.6 ± 0.6	-	-

* sum of artesunate (converted to dihydroartemisinin equivalence) and dihydroartemisinin

Mefloquine

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD	Reference (R) arithmetic mean ± SD	log-transformed parameters*	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	24.0 ± 25.2	5.5 ± 5.9	-	-
C_{max} (ng/ml)	716 ± 217	1284 ± 318	68.7	62.1 – 76.0
AUC_{0-t} (ng.h/ml)	322336 ± 113891	481369 ± 137624	82.4	74.7 – 90.9
AUC_{0-inf} (ng.h/ml)	378136 ± 124715	528414 ± 163880	-	-
T1/2 (h)	486 ± 123	532 ± 160	-	-

* dose normalised

Plasma concentrations of artesunate are subject to a high variability. Some subjects had only a few data points. This is a known phenomenon for artesunate.

The 90% CI for Cmax and AUC_{0-t} for artesunate, dihydroartemisinin and the total equivalent dihydro-artemisinin indicate that the exposure is lower after administration of the fixed dose combination compared to the Arsumax tablet.

For Cmax, mean ratio was 35%, 25% and 27% lower, respectively for the fixed dose combination, and 90% CI were outside the 80 – 125% criteria.

For AUC_{0-t}, mean ratio was 23%, 16% and 16% lower, respectively for the fixed dose combination, and 90% CI were outside the 80 – 125% criteria. No significant difference in tmax for artesunate and dihydroartemisinin was observed between both treatments.

The dose normalised 90% CI for Cmax and AUC_{0-t} for mefloquine indicate that the exposure is lower after administration of the fixed dose combination, compared to the Lariam tablet. Cmax and AUC_{0-t} mean ratio are 31% and 18%, respectively, lower for the fixed dose combination, and 90% CI were outside the 80 – 125% criteria. It should be taken into account that the intended dose is 400 mg mefloquine/day (i.e. 2 tablets) and that dose normalisation is only to be used for comparison of the fixed dose combination tablet with the loose tablets.

In the **Phase II study ASMQ-BKK**, 50 adult patients with P. falciparum malaria were randomised to receive during 3 days two fixed dose combination 100/200 mg tablets or the standard weight-based regimen used in Thailand, i.e. 4 mg/kg artesunate during 3 days and 15 mg/kg mefloquine at day 2 and 10 mg/kg at day 3. Each subject was assigned to receive one of the following two treatments in a randomized fashion:

Treatment Test: - 2 tablets artesunate/mefloquine 100/200 mg at day 1, 2 and 3
(artesunate 200 mg + mefloquine 400 mg/day)
Batch no. 070008.

Treatment Reference: - Arsumax® 50 mg
(artesunate 4 mg/kg at day 1, 2 and 3)
Batch no. 031201.
- Lariam® 250 mg
(mefloquine 15 mg/kg at day 2, and 10 mg/kg at day 3)
Batch no. B1100

The applied dose for the fixed dose combination is in accordance with the recommended dose for patients (2 tablets o.d. for 3 days).

Serial blood samples for artesunate were taken up to 12 h after administration and for mefloquine up to day 28 during each study period to obtain bioavailability characteristics.

The study was performed with 50 patients, i.e. 25 patients per group. Groups were balanced regarding age, height, weight and BMI. Data from some subjects were not included due to inadequate data points (applicable to artesunate and dihydroartemisinin) or positive pre-dose levels (applicable to mefloquine).

The pharmacokinetic variables for artesunate, dihydroartemisinin, total equivalent dihydroartemisinin and mefloquine are summarised in the following tables:

Artesunate

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD n=19	Reference (R) arithmetic mean ± SD n=23
t_{max} (h)	0.8 ± 0.7	0.9 ± 0.6
C_{max} (ng/ml)	249 ± 266	451 ± 440
AUC_{0-t} (ng.h/ml)	302 ± 307	314 ± 246
AUC_{0-inf} (ng.h/ml)	780 ± 675	582 ± 546
T1/2 (h)	1.2 ± 1.0	0.8 ± 0.4

Dihydroartemisinin

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD n=20	Reference (R) arithmetic mean ± SD n=23
t_{max} (h)	2.1 ± 1.1	1.4 ± 0.7
C_{max} (ng/ml)	1182 ± 857	2043 ± 949
AUC_{0-t} (ng.h/ml)	3141 ± 2419	3647 ± 1356
AUC_{0-inf} (ng.h/ml)	3357 ± 2855	4121 ± 1124
T1/2 (h)	1.1 ± 0.5	0.8 ± 0.2

Total equivalent Dihydroartemisinin*

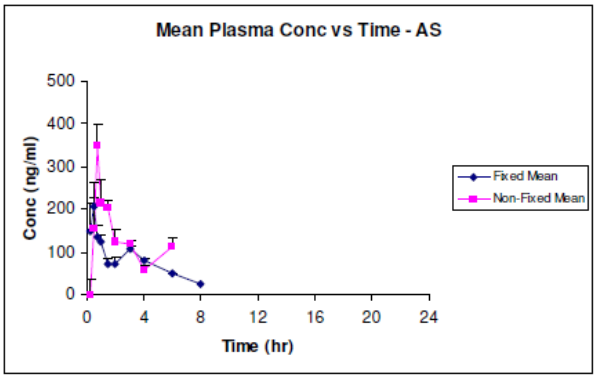
Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD	Reference (R) arithmetic mean ± SD
t_{max} (h)	1.9 ± 1.1	1.3 ± 0.7
C_{max} (ng/ml)	1291 ± 865	2215 ± 1108
AUC_{0-t} (ng.h/ml)	3209 ± 2435	3773 ± 1469
AUC_{0-inf} (ng.h/ml)	3442 ± 2799	4267 ± 1313
T1/2 (h)	1.1 ± 0.4	0.7 ± 0.2

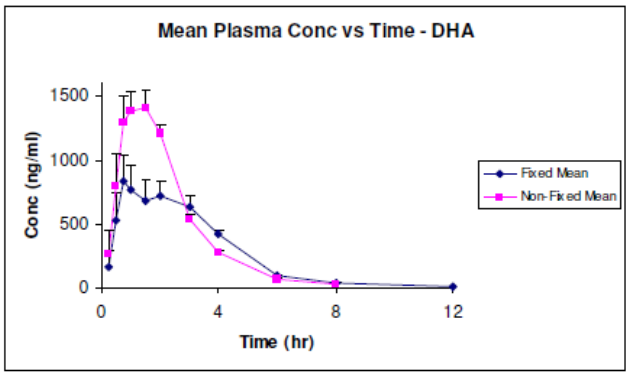
* sum of artesunate (converted to dihydroartemisinin equivalence) and dihydroartemisinin

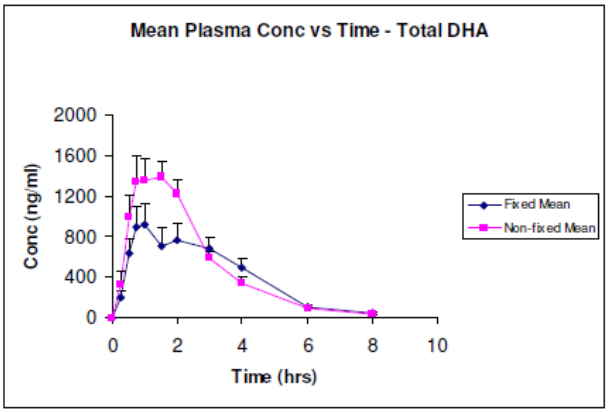
Mefloquine

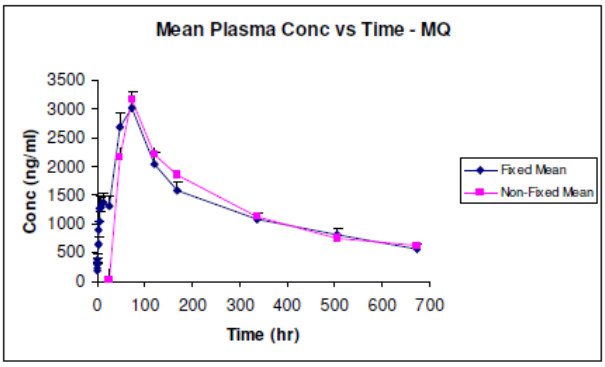
Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD n=20	Reference (R) arithmetic mean ± SD n=23
t_{max} (h)	72.0 ± 19.1	71.0 ± 13.5
C_{max} (ng/ml)	3279 ± 1252	3239 ± 734
AUC_{0-t} (ng.h/ml)	838253 ± 376738	815716 ± 230030
AUC_{0-inf} (ng.h/ml)	1193136 ± 634553	1109169 ± 364564
T1/2 (h)	286 ± 128	322 ± 114

Mean plasma concentrations are shown in the figures below.



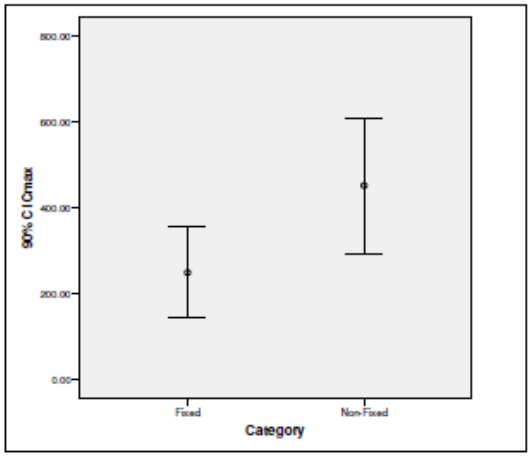


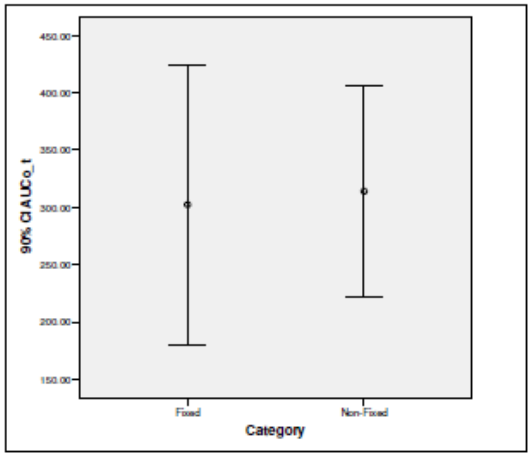




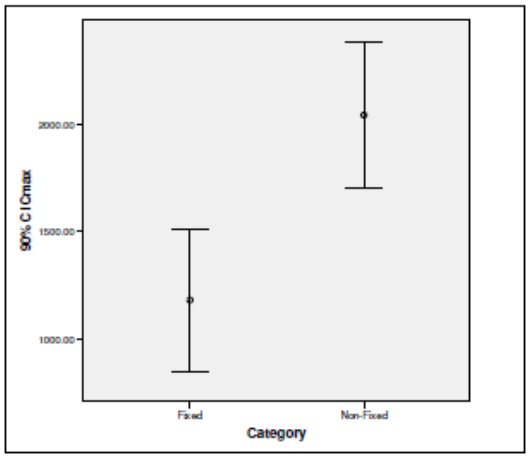
The mean and 90% confidence intervals for Cmax and AUC are shown in the figures below.

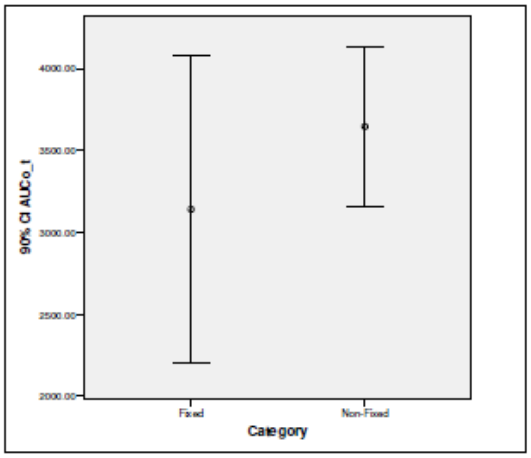
Mean and 90% confidence intervals of Cmax and AUC_{0-t} for artesunate.



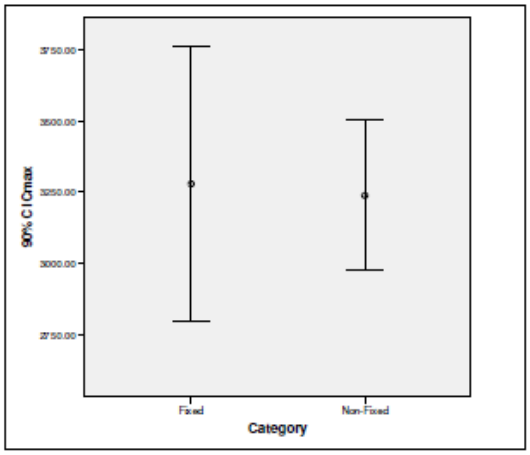


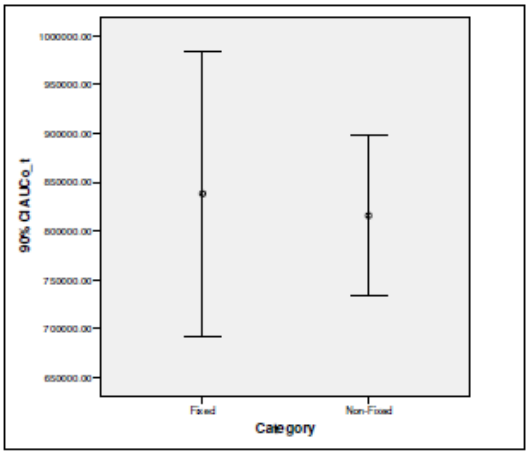
Mean and 90% confidence intervals of Cmax and AUC_{0-t} for dihydroartemisinin.





Mean and 90% confidence intervals of Cmax and AUC_{0-t} for mefloquine.





Considering the fact that the mean weights in both groups are comparable (50.1 vs 51 kg) with similar variation, for artesunate the administered dose is comparable (200 mg). Although a comparable dose was administered, at day 1 Cmax for artesunate and dihydroartemisinin were statistically significant lower (about 45%), while the AUC_{0-t} for both compounds were about 20% lower, however the latter was not statistically significant. Inter-study comparison with study ASMQ-HNV showed that the AUC of artesunate and its metabolite are considerably higher in malaria patients compared to healthy volunteers. This is in line with literature data indicating a lower artesunate clearance in malaria patients.

For mefloquine, Cmax and AUC0-t were comparable, although a higher variability is observed after administration of the fixed dose combination tablet.
At 672 h after administration, 8 and 13 subjects had mefloquine plasma levels of > 500 ng/ml after administration of the fixed dose combination tablets and the loose tablets, respectively. 500 ng/ml is considered the minimal inhibitory concentration (MIC).

In the **Phase III study DND-ASM-07**, patients (n=77) with malaria received two tablets of the 100/200 mg fixed dose combination once daily for three consecutive days. Blood samples for population pharmacokinetic analysis were taken at pre-dose, within 8 hours after the first dose, within 8 hours after the 3rd dose and within 72 hours after the first dose.
Samples were collected from 74 patients (96.1% of total) for calculation of artesunate and dihydro-artemisinin concentration and 60 patients (77.9% of total) for calculation of mefloquine concentration. A total of 534 pharmacokinetic samples were available for the study, 230 for artesunate/dihydro-artemisinin and 304 samples for mefloquine.

The population pharmacokinetic model for artesunate and dihydroartemisinin was a 1-compartment model with linear absorption and elimination, with a proportional residual error. As most of the artesunate concentrations were below the limit of quantitation, the data were combined with dihydroartemisinin. Cmax was 1511 ± 114 ng/ml and AUC_{0-inf} 4823 ± 1567 ng.h/ml which were in line with those obtained in study ASMQ-BKK.

The population pharmacokinetic model for mefloquine was a 2-compartment model with first-order absorption and elimination. The clearance was 0.37 ml/min/kg, the volume of distribution 11.9 l/kg and the elimination half-life 518 h, which were in line with those values obtained in study ASMQ-BKK (i.e. 0.4 ± 0.2 ml/min/kg, 9.1 ± 2.9 l/kg and 286 ± 128 h, respectively).

This application concerns the 25/50 mg strength for use in paediatric patients up to 6 years of age. The 25/50 mg strength is dose proportional with the 100/200 mg strength (available for use in older children, adolescents and adults). Comparability between both strengths has been further supported by comparable dissolution.

In conclusion, for the new fixed dose combination, a different dosing regimen is applied compared to the loose tablets, and lower exposures have been observed for artesunate and dihydroartemisinin. However, clinical data have been submitted to support the efficacy and safety data for this new fixed dose combination (see clinical part).

4. Summary of Product Safety and Efficacy

Introduction

To reduce the risk of resistance of *P. falciparum* and improve treatment outcomes, WHO recommends that artemisinin-based combination therapies be used for treatment of uncomplicated *falciparum* malaria[1]. The combination of the artemisinin derivative artesunate and mefloquine has been recommended by the WHO for some years, based on substantial evidence of efficacy. Nevertheless, efficacy is affected by the drug sensitivities of the local malaria parasites, and recently evidence has emerged of a decline in cure rates of artesunate plus mefloquine in Western Cambodia, as well as a slowing of parasite clearance in North-Western Thailand.
From a public health perspective, the development of fixed-dose combinations of individual antimalarials, administered together in a single dosage form, represents an important advance in the management of malaria. Fixed-dose combinations simplify treatment regimens, and are expected to improve patient adherence and facilitate implementation of interventional programs.

Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets is a fixed-dose combination of two active pharmaceutical ingredients, artesunate and mefloquine. This formulation of 25 mg artesunate and 50 mg mefloquine (as hydrochoride) is indicated for use in children from the age of 6 months to 6 years (and ≤17 kg in weight). A higher strength tablet is available containing 100 mg artesunate and 200 mg mefloquine, which allows for treatment of older children, adolescents and adults.

Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets has been developed in collaboration between the manufacturer Cipla Ltd, India and DNDi, Switzerland, a not-for-profit drug research and development organization.

Clinical Pharmacology

Pharmacodynamics

The pharmacodynamics of artesunate and mefloquine individually have been well characterized, therefore reference should be made to the SmPC (WHOPAR part 4) for a description of the pharmacodynamics of these constituents of Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Tablets.

Pharmacokinetics

The pharmacokinetics of artesunate and mefloquine have been well characterized, both when administered individually and in combination, as separate tablets. Further details are provided in the SmPC (WHOPAR part 4).

The specific pharmacokinetic parameters of Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets are described in section 3 of this report.

Clinical Efficacy and Safety

In addition to the existing data regarding the efficacy of artesunate and mefloquine used as combination therapy, evidence for the efficacy of Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets comes primarily from an open-label clinical study of 500 patients conducted in North-Western Thailand (the Mae Sot Study[2]).

The study was conducted in 2004-2005 in patients ranging in age from 6 months (and >5 kg) to 65 years. A total of 251 patients received Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets, including 65 patients ≤13 years of age and 32 patients ≤7 years of age; 249 patients received separate artesunate and mefloquine tablets, including 61 patients ≤13 years of age and 23 patients ≤7 years of age.

In the Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets group, paediatric patients weighing 5–8 kg received one 25/50mg artesunate/mefloquine (paediatric) tablet once daily for three days, those weighing 9–17 kg received two 25/50 mg tablets, those weighing 18–29 kg received one 100/200 mg (adult) tablet, and those weighing 30 kg and over received two 100/200 mg tablets. In contrast, the comparator "loose tablets" treatment group received a standard artesunate-mefloquine regimen, consisting of artesunate (Arsumax®, 50 mg tablets, Sanofi-Synthélabo, France) and mefloquine (Lariam®, 250 mg tablets, Roche). Patients received approximately 4 mg/kg/day artesunate for 3 days and 25 mg/kg mefloquine, given as 15 and 10 mg/kg/day on the second and third days of treatment, respectively.

Patients treated with Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets experienced a Day 63 PCR-corrected cure rate of 91.9% (95% CI 88.2, 95.6), while those treated with the standard loose tablet regimen of artesunate and mefloquine displayed a Day 63 PCR-corrected cure rate of 89.2% (95% CI 85.0, 93.4; Kaplan-Meier survival analysis, log-rank test for significance). Using a conventional analysis, Day 63 PCR-corrected cure rates for the Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets and separate drugs groups were 88.7% and 88.8%, respectively, for the Per Protocol population, yielding a difference (Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets - loose drugs) of -0.1% (95% CI -6.3, 6.1; p=0.9697).

With respect to secondary efficacy endpoints examined in the Mae Sot study, 72 hour parasite clearance rates were comparable for the two treatments, with no statistically significant differences observed in the frequency of persisting parasitaemia between the treatment groups (8% for the Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets group versus 6% for the loose tablets group). The number of patients remaining febrile over time was also comparable between the treatment groups (5% for both groups at 72 hours). Decreases in the proportion of patients with fever over time were also comparable between groups, as was gametocyte carriage was similar between groups. At baseline, gametocytaemia was evident in 27 (11%) patients in the Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets group and 24 (10%) of patients in the loose tablets group. Gametocytes emerged during the first week in 11 patients and 10 patients in the Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets and loose tablets groups, respectively.

While parasitological responses appeared similar across the different age and weight categories, the study was not sufficiently powered to allow for meaningful statistical comparisons.

Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets also demonstrated efficacy against *falciparum* malaria in cases due to mixed infections with *Plasmodium falciparum* and *Plasmodium vivax.* At baseline, mixed *P. falciparum* and *P. vivax* infections were seen in 22/251 patients (9%) in the {Product name} group and 24/249 patients (10%) for the loose tablets group. Of these, 11 and seven patients, respectively, had a second *P. vivax* infection during follow-up; the overall incidence of *P. vivax* infections during follow-up was 34% (95% CI 27, 41%) in theArtesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets group, compared to 20% (95% CI 15, 27%) in the separate tablets group.

No significant new safety concerns were identified during the Mae Sot study.

Other, supportive evidence for the efficacy of Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets was provided by a small, randomized open-label pharmacokinetic study of Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets in 50 adult patients

with acute, uncomplicated *P. falciparum* malaria, conducted concurrently with the Mae Sot study in the same area of Thailand (the BKK study, see also section 3 of this report). In this study, 22/24 patients (91.7%) treated with Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets exhibited a parasitological cure at Day 28, compared to 24/24 patients (100%) administered artesunate and mefloquine as separate tablets; the difference did not achieve statistical significance (p=0.48; ITT analysis). The difference between the two groups was due to 2 cases of early treatment failure in the Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets group following a single dose of medication; the failures appeared unrelated to the pharmacokinetics of the tablets.

Also reviewed was an open-label, single-arm, population pharmacokinetics study of Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets conducted in India (see also section 3 of this report). In the trial, 77 adult patients with acute, uncomplicated *P. falciparum* malaria were treated with Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets, resulting in a reported 63-day PCR-corrected parasitological cure rate of 100%. In addition, 73/74 patients (98.6%) were parasite-free by 48 hours.

Further supportive evidence for the efficacy of Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets comes from a study conducted in Myanmar in 2008-2009[3]. This study compared the efficacies of the 4 WHO recommended ACT combinations administered as FDC preparations[†], including Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets, with artesunate-mefloquine administered as loose tablets, in adults and children. Roughly 16% of patients had mixed infections with *P. vivax* and *P. falciparum* at presentation, and all patients were given a single dose of primaquine at the beginning of the study. In total, 811 patients were randomized to the 5 treatment groups, including 169 patients in the Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets group and 161 in the artesunate and mefloquine loose tablets group. At Day 63, 2 recrudescent *P. falciparum* infections were seen in the artesunate-mefloquine loose tablets group. This compares to no recrudescences in the Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets group, which included 81 patients under the age of 14 years, and 18 patients less than 5 years of age, resulting in a 100% Day 63 PCR-corrected cure rate.
All patients with mixed *P. falciparum* and *P. vivax* infections responded to treatment. Amongst patients receiving Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets, fewer cases of P. vivax were seen in follow-up to Day 63 than were observed in the artesunate-mefloquine loose tablets group (p=0.01); this was true for patients with both mixed *vivax* and *falciparum* infections as well as those with *falciparum* monoinfections.

Taken together, the evidence from these studies is considered adequate to establish comparable efficacy of Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets for the treatment of uncomplicated malaria due to *P. falciparum*, resulting either from *P. falciparum* monoinfection or mixed infections with *P. vivax*, in adults and children over 6 months of age, compared to a standard 3 day course of artesunate and mefloquine, administered as separate tablets.

During the course of the clinical development program for Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets, no new safety signals were observed and the general safety profile of the tablets was consistent with the established safety profile of artesunate and mefloquine, administered in combination as separate tablets. Thus, the clinical safety of this product is considered acceptable when guidance and restrictions presented in the Summary of Product Characteristics are followed. Reference should be made to the SmPC (WHOPAR part 4) for data on clinical safety.

[†] The WHO-recommended FDCs included artesunate-amodiaquine, artemether-lumefantrine, dihydroartemisinin-piperaquine, and artesunate-mefloquine (Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets).

5. Benefit risk assessment and overall conclusion

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC.

Pharmacokinetics

For the new fixed dose combination, a different dosing regimen is applied compared to the loose tablets, and lower exposures have been observed for artesunate and dihydroartemisinin. Clinical data have been submitted to support the efficacy and safety data for this new fixed dose combination.

Efficacy and Safety

The evidence from the submitted studies is considered adequate to establish comparable efficacy of Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets for the treatment of uncomplicated malaria due to *P. falciparum*, resulting either from *P. falciparum* monoinfection or mixed infections with *P. vivax*, in adults and children over 6 months of age, compared to a standard 3-day course of artesunate and mefloquine, administered as separate tablets.
During the course of the clinical development for Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets, no new safety signals were observed and the general safety profile of the product was consistent with the established safety profile of artesunate and mefloquine, administered in combination as separate tablets. Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets are considered safe and effective when used in accordance with the guidance and restrictions presented in the Summary of Product Characteristics.

Benefit/Risk Assessment

Based on the WHO assessment of data on quality, safety and efficacy the team of assessors considered by consensus that the benefit-risk profile of Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets tablets was acceptable for the following indication: "For the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum*", and has advised that the quality, efficacy and safety of this product allow inclusion of Artesunate/Mefloquine 25/50mg FDC (Fixed Dose Combination) Cipla Tablets, manufactured at Cipla Ltd., Patalganga, India, in the list of prequalified medicinal products.

References

[1] World Health Organization, 2010 Guidelines for the treatment of malaria - 2nd edition

[2] *Ashley E*A *et al*.An open label randomized comparison of mefloquine–artesunate as separate tablets vs. a new co-formulated combination for the treatment of uncomplicated multidrug-resistant falciparum malaria in Thailand. *Trop Med International Health* 2006;11:1653-1660.

[3]*Smithuis et al*., Effectiveness of five artemisinin combination regimens with or without primaquine in uncomplicated falciparum malaria: an open-label randomised trial. *Lancet Inf Dis* 2010; 10:673-81.