

Errata

Briefing Package

Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research, FDA

NDA 22-268

Coartem

(Artemether 20 mg/Lumefantrine 120 mg Tablets)

Applicant: Novartis Pharmaceuticals Corporation

Anti-Infective Advisory Committee Meeting

December 3, 2008

Summary of Changes

Section 3 Clinical Efficacy

Page 26, Table 8: Efficacy of Supportive Active-Controlled Studies with 4-Dose Coartem Regimen

Replace table with the new version below. Previous table reported results for the Evaluable population, whereas the new table reports results for the ITT population.

Table 8: Efficacy Results from Supportive Studies with 4-Dose Coartem Regimen – ITT population

Study No.	Group	N	Cure Rate			Time to Parasite Clearance (Median)	Parasite Reduction at 24 hours (Median)	Time to Fever Clearance (Median)
			7-day	14-day	28-day			
A007	Coartem	89	-	-	69.7%	36 hr	98.8%	18 hr
	Chloroquine	90	-	-	16.7%	60 hr	70.7%	27 hr
A011	Coartem	130	83.8%	84.1%*	-	-	97.8%	-
	Chloroquine	130	26.2%	8.6%*	-	-	59%	-
AIC04 Senegal	Coartem	36	-	100%	-	1 day**	94.3%	-
	Chloroquine	36	-	63.9%	-	2 days**	54.7%	-
AIC04 Cameroon	Coartem	30	-	93.3%	-	2 days**	76.8%	-
	Fansidar	30	-	53.3%	-	7 days**	49.2%	-
A003	Coartem	111	-	-	43.2%	40 hr	98.6%	52 hr
	Quinine	108	-	-	47.2%	77 hr	67.3%	88 hr
A014	Coartem	51	-	-	76.5%	32 hr	99.7%	24 hr
	Halofantrine	52	-	-	78.8%	48 hr	89.6%	32 hr
A004	Coartem	126	-	-	62.7%	43 hr	98.6%	32 hr
	Mefloquine	126	-	-	77.8%	66 hr	76.1%	54 hr
A005	Coartem	12	-	-	58.3%	36 hr	99.2%	-
	Quinine/ Fansidar	11	-	-	72.7%	69 hr	87.6%	-
A008	Coartem	309	-	-	73.1%	-	100%	-
	MAS	308	-	-	84.1%	-	100%	-
A010	Coartem	144	-	77.1%	-	-	99.2%	-
	Fansidar	143	-	87.4%	-	-	92.5%	-

*Based on evaluable population

** Unclear from the study reports for AIC04 Senegal and AIC04 Cameroon whether mean or median PCT was represented.

Page 34, replace ~~strikeout~~ with new text regarding Study 2401

In the evaluable population, the 28-day cure rate was > 95% in the core study and including the rich PK population. ~~The low cure rates (74%) observed in the ITT population are most likely due to the large number of patients (n=29, 19%) in the core study who were lost to follow up. Two of these patients had an unsatisfactory response to treatment but all were counted as treatment failures in the efficacy analysis.~~

New text:

The low cure rate (74%) observed in the ITT population was due to the large number of patients (n=31) with missing data in the core study; 17 of these patients were lost to follow-up.

Page 34-35 replace strikeout with new text regarding Study 2401

~~Five patients were considered treatment failures: one was withdrawn due to unsatisfactory therapeutic effect before receiving the full treatment course of Coartem; one patient did not achieve parasite clearance within 7 days, but cleared by day 10 and no other treatment was given; and three patients had recrudescence of parasites on days 22, 24 and 28 after initial clearance.~~

New text:

Eleven patients were considered treatment failures: one was withdrawn due to unsatisfactory therapeutic effect before receiving the full treatment course of Coartem; three patients did not achieve parasite clearance within 7 days, four patients received anti-malarial rescue therapy, and three patients had recrudescence of parasites on days 22, 24 and 28 after initial clearance.

Page 36, Table 19 in Section 3.6.1 Study A2403 contained incorrect percentages for the results in the 28-day cure rate in the evaluable population. The correct percentages are indicated below in bold.

Table 19: Coartem 28-day cure rate, PCT, FCT by body weight in Study A2403

	5 - < 10kg	10 - < 15kg	15 - 25kg	Total
28 day cure rate (ITT) n/N (%) [95% CI§]	133/154 (86.4) [79.9, 91.4]	94/110 (85.5) [77.5, 91.5]	41/46 (89.1) [76.4, 96.4]	268/310 (86.5) [82.1,90.1]
28 day cure rate (evaluable) n/N (%) [95% CI§]	133/149 (89.3) [83.1, 93.7]	94/107 (87.8%) [80.1, 93.4]	40/44 (90.9) [78.3, 97.5]	267/300 (89.0) [84.9, 92.3]
PCT Median* [95%CI†] 25-75 percentile* Range**	24[24, 35.4] 23.8 – 36.0 (5.3 to 68.0)	35.5[24, 35.8] 23.8 – 36.0 (7.7 to 59.9)	24[23.8-24.2] 23.7 – 35.9 (7.2 to 71.1)	24[24.0,35.4] 23.8 – 36.0 (5.3 to 71.1)
FCT Median* [95%CI†] 25-75 percentile* Range**	7.8[7.8,7.9] 7.8 – 23.8 (5.9 to 170.8)	7.9 [7.8,8.0] 7.8 - 23.6 (4.1 to 332.4)	7.8 [7.8,8.0] 7.8 – 8.4 (7.2 to 308.7)	7.8[7.8,7.9] 7.8 – 23.7 (4.1 to 332.4)

§ Exact method. * Kaplan-Meier Method. ** Not including censored times. †Based on the sign test (Brookmeyer and Crowley, 1982).

Section 5: CLINICAL SAFETY

Tables in the Briefing Package inadvertently showed results of all adverse events (AEs) rather than only treatment emergent AEs. Below are reproductions of the tables using treatment emergent AEs. Only tables which were significantly affected by this change are reproduced below. In general, trends remained intact and conclusions were not affected; the only change was the incidence of reported AEs was lower.

All tables were re-organized according to decreasing incidence in the Coartem 6-dose group.

Page 52, Table 31: Most frequently reported AEs, FDA adult pooled safety population

The most frequently reported adverse events $\geq 5\%$ in the Coartem 6-dose group are now shown.

Table 31: AEs $\geq 5\%$,* FDA adult pooled safety population

MedDRA system organ class	MedDRA preferred term	Coartem 4 dose N=787 (%)	Coartem 6 dose N=647 (%)	Mefloquine Artesunate N=280 (%)
Nervous system disorders	Headache	545 (69)	360 (56)	213 (76)
	Dizziness	418 (53)	253 (39)	203 (73)
Metabolism and nutrition disorders	Anorexia	466 (59)	260 (40)	191 (68)
General disorders and administration site conditions	Asthenia	352 (45)	243 (38)	189 (68)
	Pyrexia	0	159 (25)	44 (16)
	Chills	320 (41)	147 (23)	90 (32)
	Fatigue	252 (32)	111 (17)	100 (36)
Musculoskeletal and connective tissue disorders	Arthralgia	250 (32)	219 (34)	184 (66)
	Myalgia	247 (31)	206 (32)	151 (54)
Gastrointestinal disorders	Nausea	310 (39)	169 (26)	133 (48)
	Vomiting	216 (27)	113 (18)	72 (26)
	Abdominal pain	186 (24)	112 (17)	72 (26)
	Diarrhoea	59 (8)	46 (7)	16 (6)
Psychiatric disorders	Sleep disorder	261 (33)	144 (22)	128 (46)
Cardiac disorders	Palpitations	193 (25)	115 (18)	126 (45)
Hepatobiliary disorders	Hepatomegaly	175 (22)	59 (9)	19 (7)
Blood and lymphatic system disorders	Splenomegaly	172 (22)	57 (9)	41 (15)
Respiratory, thoracic and mediastinal disorders	Cough	33 (4)	37 (6)	3 (1)

* in the Coartem 6-dose group

Page 55, Table 34: Most frequently reported AEs, FDA pediatric pooled safety population

The most frequently reported adverse events $\geq 5\%$ in the Coartem 6-dose group are now shown.

Table 34: AEs $\geq 5\%*$, FDA pediatric pooled safety population

MedDRA system organ class	Preferred Term	Coartem 4 dose N=659 (%)	Coartem 6 dose N=1332 (%)	Mefloquine Artesunate N=150 (%)	SP N=143 (%)
General disorders and administration site conditions	Pyrexia	36 (6)	381 (29)	19 (13)	6 (4)
	Chills	175 (27)	72 (5)	61 (41)	4 (3)
	Asthenia	133 (20)	63 (5)	84 (56)	33 (23)
	Fatigue	181 (28)	46 (4)	51 (34)	0
Respiratory, thoracic and mediastinal disorders	Cough	106 (16)	302 (23)	1 (1)	14 (10)
Gastrointestinal disorders	Vomiting	188 (29)	242 (18)	62 (41)	35 (24)
	Abdominal pain	162 (25)	112 (8)	40 (27)	25 (17)
	Diarrhoea	63 (10)	100 (8)	7 (5)	12 (8)
	Nausea	146 (22)	61 (5)	57 (38)	1 (1)
Infections and infestations	Plasmodium falciparum infection	0	224 (17)	0	0
Metabolism and nutrition disorders	Anorexia	246 (37)	175 (13)	107 (71)	0
Nervous system disorders	Headache	281 (43)	168 (13)	126 (84)	27 (19)
	Dizziness	149 (23)	56 (4)	92 (61)	4 (3)
Blood and lymphatic system disorders	Splenomegaly	183 (28)	124 (9)	46 (31)	33 (23)
	Anaemia	145 (22)	115 (9)	15 (10)	76 (53)
Hepatobiliary disorders	Hepatomegaly	147 (22)	75 (6)	33 (22)	21 (15)

* in the Coartem 6-dose group

Page 59, Table 38: Most frequently reported AEs occurring in $\geq 2\%$ of adult subjects in Study A025 by treatment group

AEs occurring in the **Coartem 6-dose over 60 hours** adult patients (rather than both 60 and 96 hours), and in **$\geq 3\%$ rather than $\geq 2\%$** are shown.

Table 38: Most frequently reported AEs occurring in $\geq 3\%$ of adult patients in Study A025 by treatment group

MedDRA system organ class	Preferred term	Coartem 4 dose N=99 (%)	Coartem 6 dose (60 hours) N=88 (%)
Nervous system disorders	Headache	93 (93.9)	81 (92.1)
	Dizziness	73 (73.7)	69 (78.4)
	Clonus	5 (5.1)	8 (9.1)
	Tremor	9 (9.1)	8 (9.1)
Metabolism and nutrition disorders	Anorexia	84 (84.9)	76 (86.4)
General disorders and administration site conditions	Asthenia	83 (83.8)	67 (76.1)
	Chills	40 (40.4)	39 (44.3)
	Fatigue	30 (30.3)	38 (43.2)
Musculoskeletal and connective tissue disorders	Arthralgia	71 (71.7)	66 (75.0)
	Myalgia	76 (76.8)	66 (75.0)
Gastrointestinal disorders	Nausea	49 (49.5)	41 (46.6)
	Vomiting	31 (31.3)	33 (37.5)
	Abdominal pain	37 (37.4)	25 (28.4)
	Diarrhoea	6 (6.1)	4 (4.6)
Psychiatric disorders	Sleep disorder	44 (44.4)	39 (44.3)
Cardiac disorders	Palpitations	43 (43.4)	34 (38.6)
Blood and lymphatic system disorders	Splenomegaly	22 (22.2)	14 (15.9)
	Anaemia	6 (6.1)	6 (6.8)
Hepatobiliary disorders	Hepatomegaly	19 (19.2)	13 (14.8)
Skin and subcutaneous tissue disorders	Rash	13 (13.1)	7 (8.0)
	Pruritus	13 (13.1)	7 (8.0)
Infections and infestations	Helminthic infection	3 (3.0)	6 (6.8)
	Nasopharyngitis	2 (2.0)	5 (5.7)
	Abscess	5 (5.1)	3 (3.4)
	Pneumonia	3 (3.0)	0
Respiratory, thoracic and mediastinal disorders	Cough	3 (3.0)	2 (2.3)
	Pharyngolaryngeal pain	4 (4.0)	3 (3.4)

Page 60, Table 39: Most frequently reported AEs occurring in $\geq 2\%$ of pediatric subjects in Study A025 by treatment group

AEs occurring in the **Coartem 6-dose over 60 hours** pediatric patients (rather than both 60 and 96 hours), and in $\geq 3\%$ rather than $\geq 2\%$ (in either arm) are shown.

Table 39: Most frequently reported AEs occurring in $\geq 3\%$ of pediatric patients in Study A025 by treatment group

MedDRA system organ class	Preferred Term	Coartem 4 dose N=21 (%)	Coartem 6 dose (60 hours) N=30 (%)
Nervous system disorders	Headache	20 (95.2)	27 (90)
	Dizziness	8 (38.1)	14 (46.7)
Metabolism and nutrition disorders	Anorexia	18 (85.7)	25 (83.3)
General disorders and administration site conditions	Asthenia	10 (47.6)	17 (56.7)
	Chills	7 (33.3)	11 (36.7)
	Fatigue	4 (19.1)	5 (16.7)
Musculoskeletal and connective tissue disorders	Myalgia	11 (52.4)	15 (50.0)
	Arthralgia	6 (28.6)	10 (33.3)
Gastrointestinal disorders	Nausea	7 (33.3)	12 (40.0)
	Vomiting	9 (42.9)	9 (30.0)
	Abdominal pain	3 (14.3)	7 (23.3)
	Diarrhoea	1 (4.8)	3 (5.1)
Blood and lymphatic system disorders	Splenomegaly	7 (33.3)	10 (33.3)
	Anaemia	4 (19.1)	3 (10.0)
Hepatobiliary disorders	Hepatomegaly	3 (14.3)	9 (30.0)
Psychiatric disorders	Sleep disorder	5 (23.8)	6 (20.0)
Cardiac disorders	Palpitations	4 (19.1)	5 (16.7)
Infections and infestations	Parasitic gastroenteritis	3 (14.3)	6 (20.0)
	Pneumonia	1 (4.8)	3 (10.0)
	Helminthic infection	1 (4.8)	2 (6.7)
	Ascariasis	1 (4.8)	2 (6.7)
Skin and subcutaneous tissue disorders	Pruritus	0	2 (3.4)
Investigations	Blood potassium decreased	0	1 (3.3)
Gastrointestinal disorders	Dyspepsia	0	1 (3.3)
Renal and urinary disorders	Oliguria	0	1 (3.3)

Page 62, Table 41: AEs by Preferred Term (>2%) for pooled Studies A026 and A028

AEs \geq 3% rather than \geq 2% (either treatment arm) are shown.

Table 41: AEs \geq 3% in adult patients treated with Coartem or MAS (Studies A026 and A028)

System Organ Class	Preferred Term	Coartem Tablets N=258 (%)	Mefloquine Artesunate N=77 (%)
General disorders and administration site conditions	Pyrexia	149 (57.8)	44 (57.1)
	Asthenia	83 (32.2)	25 (32.5)
	Chills	48 (18.6)	16 (20.8)
	Fatigue	29 (11.2)	8 (10.4)
Nervous system disorders	Headache	129 (50.0)	32 (41.6)
	Dizziness	100 (38.8)	28 (36.4)
Musculoskeletal and connective tissue disorders	Arthralgia	82 (31.8)	24 (31.2)
	Myalgia	65 (25.2)	14 (18.2)
Metabolism and nutrition disorders	Anorexia	78 (30.2)	26 (33.8)
Gastrointestinal disorders	Nausea	64 (24.8)	25 (32.5)
	Abdominal pain	44 (17.1)	11 (14.3)
	Vomiting	27 (10.5)	10 (13.0)
	Diarrhoea	11 (4.3)	2 (2.6)
	Dyspepsia	10 (3.9)	4 (5.2)
Psychiatric disorders	Sleep disorder	58 (22.5)	23 (29.9)
Cardiac disorders	Palpitations	45 (17.4)	15 (19.5)
Hepatobiliary disorders	Hepatomegaly	31 (12.0)	4 (5.2)
Blood and lymphatic system disorders	Splenomegaly	22 (8.5)	8 (10.4)
Respiratory, thoracic and mediastinal disorders	Cough	12 (4.7)	1 (1.3)
	Pharyngolaryngeal pain	7 (2.7)	4 (5.2)
Skin and subcutaneous tissue disorders	Pruritus	8 (3.1)	4 (5.2)
	Rash	5 (1.9)	3 (3.9)
Injury, poisoning and procedural complications	Overdose	0	3 (3.9)

Page 63: Replace the paragraph in strikeout with the paragraph which follows.

~~The incidence of most frequently reported AEs was significantly lower in the FDA adult pooled population compared with the pooled A026/A028 population: headache 73.8% vs. 94.9%; asthenia 56.4% vs. 79%; dizziness 54.9% vs. 77.8%; pyrexia 32.3% vs. 77%. It is important to note that all PTs are consistently higher in the pooled A026/A028 population, but the most commonly reported AEs are the same in both pooled populations. This may be due to the fact that the other 6 dose studies were non-comparative. Investigators in A026 and A028 may have been more vigilant in collecting AEs from all subjects, as they knew a proportion of their randomized subjects were receiving MAS and the AE profile of mefloquine is well established. There may also have been other differences in data collection and study design differences to account for this observation.~~

AEs according to Preferred Terms $\geq 3\%$ for Coartem and MAS groups are shown in Table 41. AE rates for Coartem in the A026/A028 adult population was similar to those in the FDA pooled adult population.

Page 66, Table 44: Most frequently reported AEs by Preferred Term (>2%), pediatric pooled safety population

AEs \geq 3% rather than \geq 2% (either treatment arm) are shown.

Table 44: AEs \geq 3% in pediatric patients treated with Coartem or MAS (Studies A026 and A028)

System Organ Class	Preferred Term	Coartem Tablets N=56 (%)	Mefloquine Artesunate N=28 (%)
Nervous system disorders	Headache	37 (66.1)	14 (50.0)
	Dizziness	23 (41.1)	9 (32.1)
General disorders and administration site conditions	Pyrexia	34 (60.7)	19 (67.9)
	Asthenia	25 (44.6)	8 (28.6)
	Chills	19 (33.9)	4 (14.3)
	Fatigue	5 (8.9)	0
Metabolism and nutrition disorders	Anorexia	30 (53.6)	11 (39.3)
Gastrointestinal disorders	Vomiting	23 (41.1)	12 (42.9)
	Nausea	18 (32.1)	9 (32.1)
	Abdominal pain	17 (30.4)	9 (32.1)
	Dyspepsia	0	1 (3.6)
Blood and lymphatic system disorders	Splenomegaly	18 (32.1)	4 (14.3)
	Anaemia	4 (7.1)	2 (7.1)
Hepatobiliary disorders	Hepatomegaly	17 (30.4)	4 (14.3)
Musculoskeletal and connective tissue disorders	Arthralgia	17 (30.4)	7 (25.0)
	Myalgia	9 (16.1)	5 (17.9)
Psychiatric disorders	Sleep disorder	12 (21.4)	7 (25.0)
Cardiac disorders	Palpitations	10 (17.9)	2 (7.1)
Infections and infestations	Respiratory tract infection	2 (3.6)	0
	Nasopharyngitis	1 (1.8)	2 (7.1)
	Bronchitis	0	1 (3.6)
	Parasitic gastroenteritis	0	1 (3.6)
	Subcutaneous abscess	0	1 (3.6)
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	2 (3.6)	0
	Cough	0	1 (3.6)
	Epistaxis	0	3 (10.7)
Skin and subcutaneous tissue disorders	Urticaria	0	1 (3.6)

Page 67: Replace the paragraph in ~~strikeout~~ with the paragraph which follows.

~~In conclusion, comparator studies A026 and A028 did not show any safety findings which were significantly different than the FDA adult and pediatric pooled populations. AE rates for the most common AEs and severe AEs were generally uniformly higher in the pooled A026/A028 population, but the types of AEs reported were similar. The difference in AE incidence can be attributed to study design differences.~~

In conclusion, comparator studies A026 and A028 did not show any safety events that were not also identified in the FDA adult or FDA pediatric pooled populations. In adults, Coartem AE rates for the most common AEs and severe AEs were generally similar between the A026/A028 and FDA pooled adult population. In pediatric patients, reported Coartem AE rates were higher in the A026/A028 population compared to the FDA pooled pediatric population probably due to age differences in the pediatric patients. Pediatric patients in A026 were 2 years and older, patients in A028 were 12 years and older, whereas a large percentage of children in the FDA pooled pediatric population were very young infants (particularly Study B2303, 6-dose study) who were likely unable to articulate symptoms such as headache or dizziness.

Page 68, Table 45: Adverse events affecting the SOC “Nervous system disorders”, FDA adult pooled safety population

Table 45: Adverse events affecting the SOC “Nervous system disorders”, FDA adult pooled safety population

MedDRA preferred term	Coartem 4 dose N=787 (%)	Coartem 6 dose N=647 (%)	Mefloquine Artesunate N=280 (%)
Headache	545 (69.3)	360 (55.6)	213 (76.1)
Dizziness	418 (53.1)	253 (39.1)	203 (72.5)
Clonus	5 (0.6)	16 (2.5)	0
Tremor	23 (2.9)	16 (2.5)	13 (4.6)
Nystagmus	8 (1.0)	5 (0.8)	16 (5.7)
Hypoaesthesia	3 (0.4)	4 (0.6)	7 (2.5)
Ataxia	11 (1.4)	3 (0.5)	14 (5.0)
Somnolence	1 (0.1)	3 (0.5)	0
Fine motor delay	0	2 (0.3)	2 (0.7)
Coma	0	1 (0.2)	0
Mental impairment	0	1 (0.2)	0
Convulsion	1 (0.1)	0	0
Coordination abnormal	0	0	1 (0.4)
Dysgeusia	1 (0.1)	0	0
Hypersomnia	1 (0.1)	0	0
Lethargy	1 (0.1)	0	0
Paraesthesia	32 (4.1)	0	27 (9.6)

MedDRA preferred term	Coartem 4 dose N=787 (%)	Coartem 6 dose N=647 (%)	Mefloquine Artesunate N=280 (%)
Syncope vasovagal	1 (0.1)	0	0

Page 70, Table 47: Adverse events affecting the SOC “Nervous system disorders”, FDA pediatric pooled safety population

Table 47: Adverse events affecting the SOC “Nervous system disorders”, FDA pediatric pooled safety population

Preferred Term	Coartem 4 dose N=659 (%)	Coartem 6-dose N=1332 (%)	Mefloquine Artesunate N=150 (%)	SP N=143 (%)
Headache	281 (42.6)	168 (12.6)	126 (84.0)	27 (18.9)
Dizziness	149 (22.6)	56 (4.2)	92 (61.3)	4 (2.8)
Clonus	7 (1.1)	11 (0.8)	0	0
Hyperreflexia	2 (0.3)	6 (0.5)	0	0
Convulsion	6 (0.9)	4 (0.3)	0	0
Somnolence	2 (0.3)	4 (0.3)	0	1 (0.7)
Myoclonus	0	3 (0.2)	0	0
Tremor	3 (0.5)	2 (0.2)	1 (0.7)	0
Ataxia	3 (0.5)	1 (0.1)	5 (3.3)	0
Dyskinesia	0	1 (0.1)	2 (1.3)	0
Epilepsy	0	1 (0.1)	0	0
Nystagmus	4 (0.6)	1 (0.1)	4 (2.7)	0
Aphasia	1 (0.2)	0	0	0
Coordination abnormal	2 (0.3)	0	0	0
Facial palsy	1 (0.2)	0	0	0
Febrile convulsion	1 (0.2)	0	0	2 (1.4)
Fine motor delay	8 (1.2)	0	0	0
Hypersomnia	1 (0.2)	0	0	0
Hypokinesia	44 (6.7)	0	0	0
Hypotonia	0	0	0	1 (0.7)
Lethargy	34 (5.2)	0	0	1 (0.7)
Paraesthesia	4 (0.6)	0	4 (2.7)	0
Speech disorder	33 (5.0)	0	0	1 (0.7)