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Product name: **Combivir**
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SCIENTIFIC DISCUSSION

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SCIENTIFIC DISCUSSION

1 Introduction

There is a need for anti-HIV drugs for children acknowledged by a number of organisations including WHO and UNICEF. In response to these calls the Paediatric Expert Group (PEG), created by the CPMP in July 2001, completed an assessment of the paediatric needs for anti-HIV drugs in Europe. In this evaluation numerous limitations were identified which could damage treatment compliance in children. Oral solutions have limitations insofar as they often present a bad taste; they require large volumes in older children; they may contain some excipients hazardous for children and they present some logistic problems (small bottles, refrigeration…). These limitations are especially critical in resource-poor settings. As a conclusion of this evaluation, it was considered that the Marketing Authorisation Holders (MAHs) should be further encouraged to develop small tablets with lower strength for children able to swallow tablets and GSK was informed of this request in 2004. As a response, the MAH proposed to pursue the development of **scored tablets** for Combivir tablets, which is the scope of this submission.

This Type II variation concerns the MAH's proposal to extend the approved indication to register Combivir scored tablet formulation intended for **use in children weighting 14 kg or more**.

The proposed indication is:
"Combivir is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection (see section 4.2)."

The proposed posology for this new Combivir formulation is:

Children weight	**Posology**
Children weighing **at least 30 kg**	One whole tablet twice daily
Children weighing **between 21 kg to 30 kg**	One half tablet in the morning One whole tablet in the evening
Children weighing **between 14 kg to 21 kg**	One half tablet twice daily

These proposed dosing recommendations for lamivudine in the fixed-dose combination Combivir tablet are consistent with those approved for paediatric use of Epivir (lamivudine) tablets.

The currently approved dosing recommendations for Retrovir (zidovudine) for paediatric use are based **on body surface area (BSA) and dosed three times daily.**
The MAH proposes to switch from a three times daily dosage based on BSA to a **twice daily zidovudine dosage based on body weight**.
The MAH proposed to submit an EU Mutual Recognition Type II variation to update the Retrovir product information with the new zidovudine dosage regimen, once the variation for this extension of indication for Combivir scored tablets is approved.

The **proposed Combivir scored tablets are identical to the current non-scored tablets** except for the addition of the breakline and introduction of the mark on both sides. The MAH has planned to replace the non-scored tablets by the scored tablets, as soon as this new formulation will be approved.

Furthermore, the MAH proposes to update section 5.2 "Pharmacokinetic properties" of the SPC to be harmonised with the Product Information (PI) of Epivir and Retrovir and to include new pharmacokinetic data on children.

This variation includes Quality and Clinical data. **No new clinical data has been generated in support of the scored tablet application**; existing data have merely been re-analysed to determine suitable paediatric doses.

2 Quality aspects

The MAH applied to register scored Combivir tablets. It is the MAH's intention to replace the currently registered non-scored tablets with the scored Combivir tablets. The proposed tablets are white to off-white, capsule-shaped film-coated tablets engraved with "GXFC3" and with a score line on each face of the tablet.

The introduction of the score line and additional engraving will result only in a change of appearance of the tablets (no changes to the qualitative or quantitative composition of the finished product were proposed). Batch analysis data and dissolution profile results indicate that the addition of the score line has not compromised product quality. The formulation composition and processing conditions of commercial scale for tablets with the selected breakline meet the specifications of the commercial non-scored tablets. The proposed scored tablets are equivalent to currently marketed non-scored tablets. The proposed change has been supported by appropriate pharmaceutical development (selection of breakline design), process validation and stability studies.

3 Non-clinical aspects

3.1 Environmental Risk Assessment

Scored tablets are intended to replace the non-scored tablets or the use of liquid formulations of lamivudine and zidovudine. Therefore in agreement with the MAH proposal the CHMP concluded that there was no relevant additional environmental burden associated with this submission.

4 Clinical aspects

4.1 Clinical efficacy

Combivir (150 mg lamivudine plus 300 mg zidovudine) is not currently indicated for use in HIV-infected paediatric patients less than 12 years old of age because it is a fixed-dose combination that cannot be adjusted based on body size for this patient population.

The currently recommended dosage for zidovudine and lamivudine in paediatrics are:

- **zidovudine** (children from **3 months to 12 years** of age): **360 to 480 mg/m² per day**, **in 3 or 4 divided doses**. The maximum dosage should not exceed 200 mg every 6 hours. Of note, the recommended dose in adults is 500 or 600 mg/day in 2 or 3 divided doses.
- **lamivudine** (children from **3 months to 12 years** of age): **4 mg/kg twice daily, up to a maximum of 300 mg daily.**

Based on the re-analysis of existing data the MAH has proposed for Combivir tablets the following posology:

Children weight	**Posology**
Children weighing **at least 30 kg**	One whole tablet twice daily
Children weighing **between 21 kg to 30 kg**	One half tablet in the morning One whole tablet in the evening
Children weighing **between 14 kg to 21 kg**	One half tablet twice daily

4.1.1 Zidovudine

4.1.1.1 Change from zidovudine BSA-based to weight based dosing

Weight-based are simplified regimens and therefore the MAH proposed to switch from a BSA-based dosing for zidovudine to a weight-based dosing. For this purpose, the MAH has first extracted the values of height at the 5th, 50th, and 95th percentile for a given body weight from the CDC Growth Charts and then determined the corresponding BSA values for a given body weight, using various

calculation methods. Among these calculation functions, the Mosteller equation (see table 1) is the one preferred by UNICEF/WHO, as it is the easiest to use.

Table 1 Mosteller Equation

Body	HT (cm) Values at Percentile for WT			BSA (m2) Values at Percentile for WT			Daily ZDV dose (mg) from 480mg/m2/day at BSA Percentiles			Daily ZDV dose (mg) from 360mg/m2/day at BSA Percentiles			Range in Daily ZDV Dose (mg)		Daily ZDV Dose (mg) from Stated mg/kg Total Daily Dose					
WT (kg)	5th	50th	95th	5th	50th	95th	5th	50th	95th	5th	50th	95th	Min	Max	30	24	22.5	18	15	12
4	49	53	57	0.233	0.243	0.252	111.8	116.6	121.0	83.9	87.5	90.7	83.9	121.0	120	96	90	72	60	48
5	53	57	61	0.271	0.281	0.291	130.1	134.9	139.7	97.6	101.2	104.8	97.6	139.7	150	120	113	90	75	60
6	57	61	65	0.308	0.319	0.329	147.8	153.1	157.9	110.9	114.8	118.4	110.9	157.9	180	144	135	108	90	72
7	60	65	69	0.342	0.356	0.366	164.2	170.9	175.7	123.1	128.2	131.8	123.1	175.7	210	168	158	126	105	84
8	64	68	72	0.377	0.389	0.400	181.0	186.7	192.0	135.7	140.0	144.0	135.7	192.0	240	192	180	144	120	96
9	67	72	76	0.409	0.424	0.436	196.3	203.5	209.3	147.2	152.6	157.0	147.2	209.3	270	216	203	162	135	108
10	71	76	81	0.444	0.459	0.474	213.1	220.3	227.5	159.8	165.2	170.6	159.8	227.5	300	240	225	180	150	120
11	75	81	85	0.479	0.497	0.510	229.9	238.6	244.8	172.4	178.9	183.6	172.4	244.8	330	264	248	198	165	132
12	80	86	91	0.516	0.535	0.551	247.7	256.8	264.5	185.8	192.6	198.4	185.8	264.5	360	288	270	216	180	144
13	85	90	97	0.554	0.570	0.592	265.9	273.6	284.2	199.4	205.2	213.1	199.4	284.2	390	312	293	234	195	156
14	87	94	100	0.582	0.605	0.624	279.4	290.4	299.5	209.5	217.8	224.6	209.5	299.5	420	336	315	252	210	168
15	91	98	105	0.616	0.639	0.661	295.7	306.7	317.3	221.8	230.0	238.0	221.8	317.3	450	360	338	270	225	180
16	94	102	108	0.646	0.673	0.693	310.1	323.0	332.6	232.6	242.3	249.5	232.6	332.6	480	384	360	288	240	192
17	97	105	112	0.677	0.704	0.727	325.0	337.9	349.0	243.7	253.4	261.7	243.7	349.0	510	408	383	306	255	204
18	100	109	116	0.707	0.738	0.762	339.4	354.2	365.8	254.5	265.7	274.3	254.5	365.8	540	432	405	324	270	216
19	103	111	120	0.737	0.765	0.796	353.8	367.2	382.1	265.3	275.4	286.6	265.3	382.1	570	456	428	342	285	228
20	105	114	123	0.764	0.796	0.827	366.7	382.1	397.0	275.0	286.6	297.7	275.0	397.0	600	480	450	360	300	240
21	108	117	126	0.794	0.826	0.857	381.1	396.5	411.4	285.8	297.4	308.5	285.8	411.4		504	473	378	315	252
22	111	119	130	0.824	0.853	0.891	395.5	409.4	427.7	296.6	307.1	320.8	296.6	427.7		528	495	396	330	264
23	113	122	131	0.850	0.883	0.915	408.0	423.8	439.2	306.0	317.9	329.4	306.0	439.2		552	518	414	345	276
24	115	125	134	0.876	0.913	0.945	420.5	438.2	453.6	315.4	328.7	340.2	315.4	453.6		576	540	432	360	288
25	117	126	136	0.901	0.935	0.972	432.5	448.8	466.6	324.4	336.6	349.9	324.4	466.6		600	563	450	375	300
26	119	128	138	0.927	0.961	0.998	445.0	461.3	479.0	333.7	346.0	359.3	333.7	479.0			585	468	390	312
27	120	130	140	0.949	0.987	1.025	455.5	473.8	492.0	341.6	355.3	369.0	341.6	492.0			608	486	405	324
28	122	132	142	0.974	1.013	1.051	467.5	486.2	504.5	350.6	364.7	378.4	350.6	504.5				504	420	336
29	123	133	144	0.995	1.035	1.077	477.6	496.8	517.0	358.2	372.6	387.7	358.2	517.0				522	435	348
30	124	134	145	1.017	1.057	1.099	488.2	507.4	527.5	366.1	380.5	395.6	366.1	527.5				540	450	360
31	125	135	147	1.037	1.078	1.125	497.8	517.4	540.0	373.3	388.1	405.0	373.3	540.0				558	465	372
32	126	137	148	1.058	1.104	1.147	507.8	529.9	550.6	380.9	397.4	412.9	380.9	550.6				576	480	384
33	128	138	150	1.083	1.125	1.173	519.8	540.0	563.0	389.9	405.0	422.3	389.9	563.0				594	495	396
34	129	139	152	1.104	1.146	1.198	529.9	550.1	575.0	397.4	412.6	431.3	397.4	575.0				612	510	408
35	129	141	153	1.120	1.171	1.220	537.6	562.1	585.6	403.2	421.6	439.2	403.2	585.6					525	420
36	131	142	154	1.145	1.192	1.241	549.6	572.2	595.7	412.2	429.1	446.8	412.2	595.7					540	432
37	132	144	156	1.165	1.217	1.266	559.2	584.2	607.7	419.4	438.1	455.8	419.4	600.0					555	444
38	133	145	157	1.185	1.237	1.287	568.8	593.8	617.8	426.6	445.3	463.3	426.6	600.0					570	456
39	134	147	159	1.205	1.262	1.312	578.4	605.8	629.8	433.8	454.3	472.3	433.8	600.0					585	468
40	136	148	160	1.229	1.282	1.333	589.9	615.4	639.8	442.4	461.5	479.9	442.4	600.0					600	480

Then, the daily zidovudine doses base on the approved regimens (360 to 480 mg/m² daily) were calculated. Based on these results a proposal was made for daily mg/kg zidovudine doses, which are within the range from 360mg/m²/day at the 5th percentile BSA to 480mg/m²/day at the 95th percentile:

Body weight	**Zidovudine regimen**
4 to < 9 kg	24 mg/kg/day (8 mg/kg TID)
≥ 9 to < 30 kg	18 mg/kg/day (6 mg/kg TID)
≥ 30 kg*	200 mg TID (approved dose for ≥ 12 years old)

* 30 kg is the 5th percentile of body weight for 12 years old
TID: three times a day

4.1.1.2 Change from zidovudine dosing three times per day to twice daily

The MAH did not provide any new efficacy clinical data to support the change from the approved three or four times daily dosing of zidovudine to the proposed twice daily dosing. Only a pharmacokinetic study conducted in 6 HIV-infected children from 2 to 13 years of age together with new analysis of the available data was submitted by the MAH. Table 2 summarises the results of this pharmacokinetic study.

Table 2 Summary of zidovudine pharmacokinetic parameter estimates and within-subject parameter rations from zidovudine administration twice daily vs three times daily [a]

Zidovudine Pharmacokinetic Parameter	Zidovudine Dosage Regimen		Within-Subject q12h to q8h Ratio
	120mg/m² q8h	180mg/m² q12h	
AUC(0-24) (h.mg/l)	5.24 (3.73 – 7.35)	4.72 (3.50 – 6.36)	0.90 (0.52 – 1.56)
Cmax (mg/l)	0.96 (0.55 – 1.70)	1.04 (0.69 – 1.57)	1.08 (0.62 – 1.88)
t½ (h)	1.31 (0.99 – 1.72)	1.15 (0.90 – 1.47)	0.88 (0.71 – 1.10)

[a]All values denote geometric mean and 90% confidence interval
q8h: corresponds to TID; q12h: corresponds to BID

The results indicate that a TID and a BID (twice a day) regimen of zidovudine show comparable pharmacokinetics profiles. However, the demonstration is only based on data derived from 6 patients. Moreover, given the pharmacodynamic properties of zidovudine, active after an intracellular phosphorylation, it would have been of value to have intracellular pharmacokinetic data collected.

To further substantiate the twice-daily regimen for zidovudine proposed for children, the MAH states that the safety and efficacy of twice daily dosing in adults is well established and that in children with more than 5-6 months of age, the pharmacokinetic profile of zidovudine is similar to that in adults (with similar plasma terminal elimination half-life (about 1.5 hours) and similar process of intracellular phosphorylation). Moreover, the MAH argues that clinical studies as CNAA3006[1] and PENTA 5[2] have investigated zidovudine as a twice daily regimen in children.

Therefore, the following weight-based zidovudine doses for twice daily regimens are proposed by the MAH, based on maintenance of the same total daily dose (e.g., 240mg/m² BID vs 160mg/m² TID, or 180mg/m² BID vs 120mg/m² TID):

Body weight	Zidovudine regimen (BID)
4 to < 9 kg	24 mg/kg/day (12 mg/kg BID)
≥ 9 to < 30 kg	18 mg/kg/day (9 mg/kg BID)
≥ 30 kg*	300 mg BID (approved dose for ≥ 12 years old)

*30 kg is the 5th percentile of body weight for 12 years old

To support its proposal, the MAH underlined that the PENTA group[3] and the WHO have developed treatment guidelines with a zidovudine regimen based on a twice daily administration.

[1] Study CNAA3006 evaluated the efficacy and safety of zidovudine 180 mg/m² twice daily plus lamivudine 4 mg/kg twice daily, with or without abacavir over 48 weeks in 205 children ranging at enrolment from 0.6 to 13 years of age.
[2] Penta 5 study evaluated safety and efficacy over 48 weeks in children from 0.3 to 16.5 years of age.
[3] Penta group: Paediatric European Network for Treatment AIDS

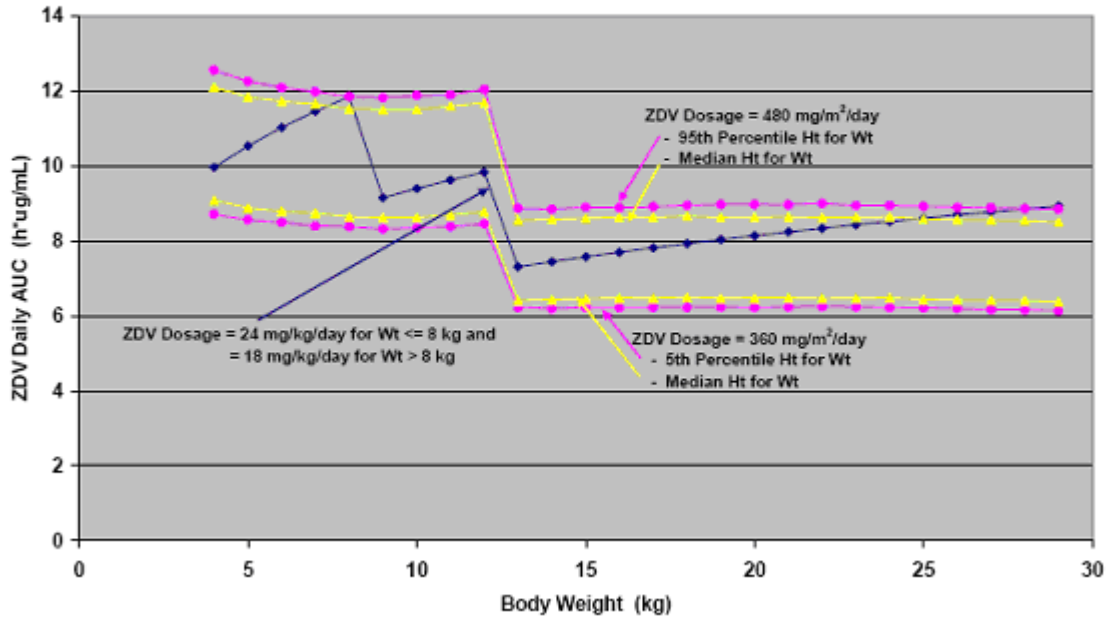
Weight-based twice daily regimen for zidovudine: study PACTG 152

In order to further substantiate the weight-based twice daily regimen for zidovudine, the MAH has provided estimates of pharmacokinetics data (AUC and Cmax) for zidovudine obtained from different calculations derived from a population pharmacokinetic model obtained from a population pharmacokinetic analysis of data in study PACTG 152 (in which two regimens of zidovudine were explored:180 mg/m² and 120 mg/m², every 6 hours).

The exposures (daily AUC) from both mg/m² and mg/kg dosing were calculated using weight-based clearance values from the model.

The figure below shows that the calculated AUCs on a weight-based dosing regimen are comprised within the range of calculated AUC on a BSA-based dosing regimen The two drops in AUC are due to the change in proposed dose recommendation at 8 kg body weight and to a step function at 12 kg (taken as typical weight for a 2-year old) for the effect of age in the clearance model.

Figure 1 **Estimated ZDV Daily AUC from Proposed Weight-based ZDV Regimens and from Approved BSA-based Regimens using Population PK Model for CL/F from PACTG-152**



Monte Carlo simulations were performed to predict zidovudine exposures (daily AUC and steady-state Cmax) for the proposed weight-based (mg/kg) doses in children using this population PK model. The results are presented in table 3 below.

Table 3 Comparison of Simulated Zidovudine Exposures in Children Receiving Proposed Weight – Based Dosing

Study	Simulation 1	Simulation 2	Simulation 3	Simulation 4	Simulation 5	Simulation 6	Historical
Population	Paediatric	Paediatric	Paediatric	Paediatric	Paediatric	Paediatric	Adult [1]
Range of Body Weight (kg)	4 to <9 kg	4 to <9 kg	9 to <13 kg	9 to <13 kg	9 to <30 kg	9 to <30 kg	NA
Age	< 2 years	< 2 years	< 2 years	< 2 years	> 2 years	> 2 years	NA
Formulation/ dose/ frequency	ZDV Syrup/ 8mg/ kg/ q8h	ZDV Syrup/ 12mg/kg/ q12h	ZDV Syrup/ 6mg/kg/ q8h	ZDV Syrup/ 9mg/kg/ q12h	ZDV Syrup/ 6mg/kg/ q8h	ZDV Syrup/ 9mg/kg/ q12h	300 mg tablet BID
# of Simulations	1000	1000	1000	1000	1000	1000	NA
AUC0-24ss, µg.h/ml							
Geo Mean (CV%)	10.7 (51%)	11.0 (55%)	9.34 (48%)	9.61 (54%)	7.46 (52%)	7.29 (52%)	
Mean (CV%)	12.0 (50%)	12.6 (56%)	10.4 (46%)	10.9 (53%)	8.42 (52%)	8.21 (52%)	4.8% (29%)
Median	10.9	10.8	9.44	9.87	7.57	7.29	
10^{th} Percentile	5.73	5.56	5.11	4.99	3.92	3.89	
90^{th} Percentile	19.3	20.8	16.8	18.4	13.8	13.6	
Cmax, ug/ml							
Geo Mean (CV%)	3.07 (45%)	4.26 (50%)	2.40 (48%)	3.36 (49%)	2.31 (49%)	3.07 (48%)	
Mean (CV%)	3.37 (45%)	4.78 (52%)	2.65 (47%)	3.75 (49%)	2.58 (50%)	3.41 (49%)	2.01[2] (40%)
Median	3.10	4.20	2.38	3.37	2.28	3.06	
10^{th} Percentile	1.78	2.34	1.35	1.84	1.30	1.69	
90^{th} Percentile	5.37	7.83	4.34	6.04	4.26	5.38	

1. Adult data (N=24) [Study NZTA1001 GSK Study report No. RM1997/00456/00]
2. Cmax = that from single dose: value is applicable due to short ZDV half life and negligible accumulation with BID dosing
ZDV: zidovudine

Post-hoc pharmacokinetic parameter estimates from individual patients were used to calculate AUC and Cmax for both BSA and body-weight based dosing

The AUC value was increased by about 2 to 3 fold in children compared to historical data in adults (study NZTA101[4]). The Cmax value was also increased in children compared to historical data in adults. The MAH explains this finding by the larger variability observed in paediatric patients.
As expected, the Cmax values were higher for the twice daily regimen than for the three times daily regimen.

The MAH has performed new simulations based on the revised population PK model. The results are presented in the table below.

[4] Study NZTA101: pivotal bioequivalence trial conducted in 24 adults receiving 300 mg zidovudine BID

Table 4 **Comparison of Zidovudine Exposure (Geometric mean [CV%]) following Proposed Weight-based Dosing Predicted by Monte Carlo Simulation (Revised and Old) Compared to Re-analysis of P53-04 and PACTG 152**

Scenario	Scenario 1	Scenario 2	Scenario 3		Scenario 4		Scenario 5	Scenario 6
Population	Paediatric	Paediatric	Paediatric		Paediatric		Paediatric	Paediatric
Range of Body Weight (kg)	4 to <9 kg	4 to <9 kg	9 to <30 kg		9 to <30 kg		>30 kg	>30 kg
Formulation/ dose/ frequency	ZDV Syrup/ 8mg/kg/ q8h	ZDV Syrup/ 12mg/kg/ q12h	ZDV Syrup/ 6mg/kg/ q8h		ZDV Syrup/ 9mg/kg/ q12h		200mg q8h	300mg q12h
Geometric mean [CV%] AUC0-24ss, μg.h/mL								
Monte Carlo Simulation (old)	10.7 (51)	11.0 (55)	<2yr[1] 9.34 (48)	>2yr[2] 7.46 (52)	<2yr[1] 9.61 (54)	>2yr[2] 7.29 (52)	NA	NA
Monte Carlo Simulation (revised)	8.51 (42)	8.33 (42)	<2yr[1] 7.40 (43)	>2yr[2] 7.39 (43)	<2yr[1] 7.32 (41)	>2yr[2] 7.39 (42)		
Reanalysis of P53-04	8.4 (n=2)	8.4 (n=2)	6.0 (54)		6.0 (54)		9.9 (n=2)	9.9 (n=2)
Reanalysis of PACTG 152	9.12 (36)	9.12 (36)	5.89 (39)		5.89 (39)		5.67 (54)	5.67 (54)
	Historical adults[3] (mean, [CV%, dosing]): 4.8 (29, 300mg q12h); Historical paediatric[4] (geometric mean,[CV%, dosing]): 5.2 (51,120mg/m^2 q8h); 7.0 (51,160mg/m^2 q8h)							
Geometric mean [CV%] Cmax, ug/mL								
Monte Carlo Simulation (old)	3.07 (45)	4.26 (50)	<2yr[1] 2.40 (48)	>2yr: 2.31 (49)	<2yr[1] 3.36 (49)	>2yr: 3.07 (48)	NA	NA
Monte Carlo Simulation(new)	2.69 (46)	3.56 (50)	<2yr[1] 2.07 (47)	>2yr[2] 2.10 (48)	<2y[1]r 2.80 (49)	>2yr[2] 2.83 (49)		
Reanalysis of P53-04	1.2 (n=2)	1.8 (n=2)	1.5 (69)		2.2 (69)		1.4 (n=2)	2.1 (n=2)
Reanalysis of PACTG 152	1.83 (29)	2.74 (29)	1.25 (32)		1.87 (32)		1.0 (44)	1.5 (44)
	Historical adults[3]: 2.01[5](40, 300mg q12h); Historical paediatric[4](geometric mean, [CV%, dosing]): 1.2 (65, 120mg/m^2 q8h); 1.6 (65, 160mg/m^2 q8h)							

The results are better in line with the results extracted from reanalyses of clinical studies. Moreover, the revised model confirms the high Cmax values.

Discussion

Change from zidovudine BSA-based to weight based dosing

The CHMP agrees that dosing recommendations based on body-weight are preferred to those based on BSA for practical reasons. Based to the MAH's demonstration the switch from BSA to weight based dosing regimen can be accepted.

Change from zidovudine dosing three times per day to twice daily
The results indicate that a TID and a BID regimen of zidovudine show comparable pharmacokinetics profiles. However, the demonstration is only based on data derived from 6 patients. Moreover, given the pharmacodynamic properties of zidovudine, active after an intracellular phosphorylation, it would have been of value to have intracellular pharmacokinetic data collected.

The CHMP recognises that the BID regimen of zidovudine in paediatric patients is widely used in clinical practice and the recent WHO/PENTA support has reinforced such an use, as well as national guidelines. However, it is regrettable that the MAH could not provide clinical efficacy data to substantiate the proposed new dosage recommendations for zidovudine in children (as regards the twice daily regimen and the BSA-dosed dosing).

The pharmacokinetic data for zidovudine were reassuring. However, the calculations of pharmacokinetic parameters for study PACTG 152 for zidovudine showed that the AUC value was increased by about 2 to 3 fold in children compared to historical data in adults (study NZTA101, a pivotal bioequivalence trial conducted in 24 adults receiving 300 mg zidovudine BID).
The MAH 's explanation for the simulated 2-3 fold increased exposure of zidovudine was an observed increased variability in the paediatric population. As could be seen from the simulations in table 3 the variability was higher in the paediatric groups (simulated variability in AUC around 50%CV as compared to 29%CV observed in adults. It is difficult to see that the difference in variability could explain a 2-3 fold difference in mean AUC.

Upon CHMP request the MAH has performed different analyses and compared results to observed exposure in children with the currently approved dose recommendations and to adult exposure, including inter-individual variability. The results confirm the high Cmax values for zidovudine in children. These findings pointed out the usefulness to perform clinical studies in special populations such as paediatric patients. Pharmacokinetic simulations might not always be sufficient to provide reassurance on efficacy and safety, as the optimal model might be difficult to define.

4.1.2 Lamivudine

Lamivudine pharmacokinetics in paediatric patients is in general similar to adults. However, two characteristics deserve to be underlined:

-Absolute bioavailabilty is reduced in paediatric patients below 12 years of age (F ranging from 55 to 65%) compared to adult patients (F ranging from 80 to 85%).

-Systemic clearance is higher in younger patients and decreased with age, approaching values around 12 years of age.

Recent findings from study NUCA2002 (included in the original paediatric MAA submission) and from the recent study PENTA 13[5] have shown that patients below 6 years of age presented AUC values reduced by 30% compared with other age groups. These findings gave rise to an update of section 5.2 of the SPC for Epivir (variation II/61, positive Opinion adopted in January 2007, by CHMP).

In order to further investigate whether certain age groups of paediatric patients have poorer oral absorption of solid oral formulations compared to liquids, pharmacokinetic data from original paediatric lamivudine trial, NUCA2002, was re-examined. In this study absolute bioavailability of lamivudine in paediatric patients was determined with patients receiving single doses of either an oral solution, capsule, and tablet formulation compared to an intravenous formulation. A scatterplot of absolute bioavailability versus age for the different formulations is shown in figure 2.

[5] PENTA13: open label cross-over 28 week pharmacokinetic study comparing the once versus twice daily lamivudine and abacavir where one or both drugs are being taken as part of combination antiretroviral therapy

Figure 2 Absolute Oral Bioavailability (F) versus Age by Formulation

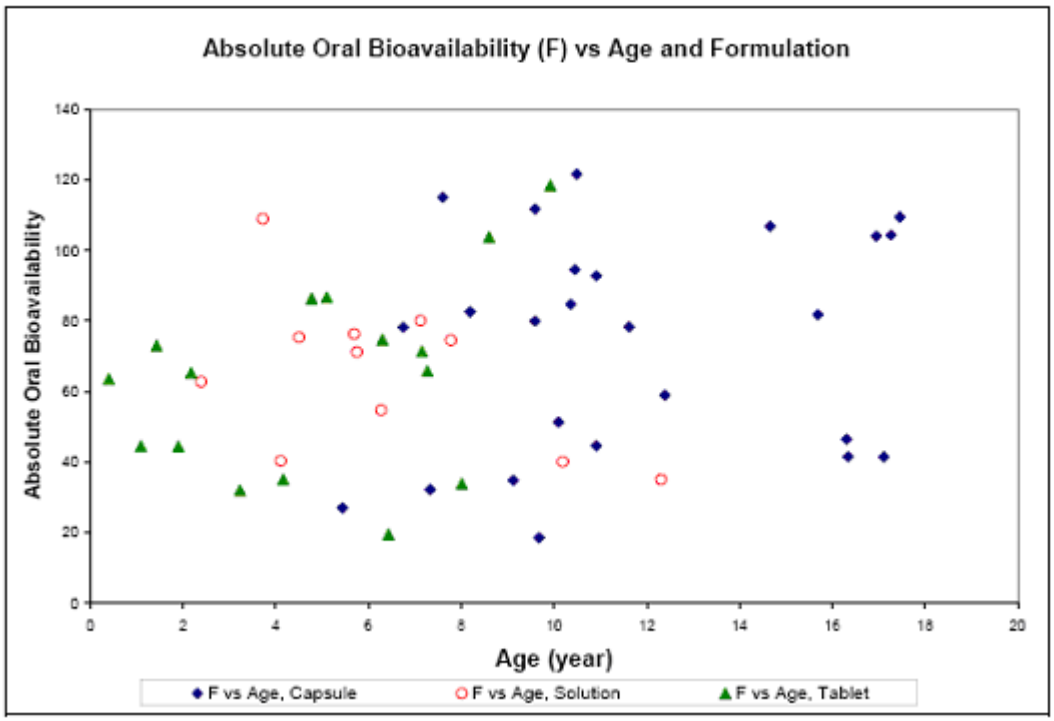


Figure 2 shows that when presenting the oral bioavailability by formulation and by age, there is a trend for increased oral bioavailability with age. As regards the value of bioavailability as a function of formulation, no clear trend is apparent.

4.1.3 Dosing recommendations for use of Combivir scored tablets in paediatrics

From the daily zidovudine doses calculated in table 1, and based on a twice daily regimen, it appears that the 150 mg zidovudine contained in a half-tablet of Combivir would be an appropriate dose for children weighing from about 14 to 22 kg.

As regards lamivudine, over the 14 to 22 kg weight range, a 75 mg lamivudine dose contained in a half-tablet of Combivir would deviate from the nominal 4 mg/kg dose by +34% at the low end of the body weight range (14 kg) and by -15% at the high end of the weight range (22 kg). To avoid a dose that is more than about 10% below the nominal 4 mg/kg dose, the upper weight limit was decreased to 21 kg. Because of the favourable safety profile of lamivudine, there is no concern in exceeding the nominal dose by 34% at the lower end of the proposed weight range (14 kg).

Similarly, it is proposed that patients weighing at least 30 kg may safely receive the full 150 mg tablet dose of lamivudine twice daily (+25% compared to the 4 mg/kg recommended dose).

In order to explore the dosing recommendations for Combivir, the MAH has performed Monte Carlo simulations based on population pharmacokinetic modelling to estimate the exposures of zidovudine and lamivudine for the following Combivir regimens:

Regimen/ Body weight	**14 to ≤ 21 kg**	**>21 to 30 kg**
Regimen 1	One half tablet twice daily	
Regimen 2		One half tablet AM One whole tablet PM
Regimen 3		One half tablet three times daily

The results of these simulations are presented in table 5.

Table 5 Comparison of Simulated Steady-State 3TC/ZDV Exposures in Children Taking Scored Combivir Tablets of Various Dosing Regimens

Study	**Simulation 1 (Reference Group)**	**Simulation 2**	**Simulation 3**
Population	Paediatric	Paediatric	Paediatric
Range of Body Weight (kg)	14-21	>21-30	>21-30
Formulation (3TC/ZDV dose)/ frequency	Half Tab (75/150 mg) q12h	Half Tab (75/150 mg) AM and full Tab (150/300mg 8 hours later	Half Tab (75/150 mg) q8h
N (# simulated individuals	1000	1000	1000
Lamivudine			
AUCO-24ss µg.h/ml			
Geo Mean (CV%)	10.2 (33%)	12.7 (40%)	12.8 (42%)
Mean (CV%)	10.7 (27.6%)	13.4 (28.8%)	13.5 (27.0%)
Median	10.6	13.0	13.4
10th Percentile	7.20	9.28	9.58
90th Percentile	14.3	18.4	18.0
Cmax, ug/mL			
Geo Mean (CV%)	1.24 (49%)	1.62 (58%)	1.45 (54%)
Mean (CV%)	1.37 (46.5%)	1.85 (55.4%)	1.61 (43.9%)
Median	1.26	1.62	1.47
10th Percentile	0.73	0.94	0.92
90th Percentile	2.19	2.98	2.45
Zidovudine			
AUCO-24ss µg.h/ml			
Geo Mean (CV%)	7.03.(53%)	7.94 (53%)	7.77 (53%)
Mean (CV%)	7.95 (52%)	8.97 (53%)	8.79 (52%)
Median	7.07	8.05	7.90
10th Percentile	3.66	4.20	3.99
90th Percentile	13.6	15.1	14.7
Cmax, ug/ml			
Geo Mean (CV%)	2.94 (52%)	3.63 (52%)	2.24 (49%)
Mean (CV%)	3.31 (53%)	4.08 (49%)	2.50 (50%)
Median	2.95	3.72	2.22
10th Percentile	1.60	1.91	1.21
90th Percentile	5.45	6.63	4.07

3TC: Lamivudine

The results of the simulations showed for both actives and regardless of dosing regimen that AUCs were slightly increased in the > 21-30 kg group compared to the 14-21 kg group.

As expected the Cmaxs were higher in the regimen 2 (0.5 tablet AM + 1 tablet PM) than in the regimen 3 (0.5 tablet three time a day). The MAH has discussed the potential alteration of the safety profile related to the higher Cmax values. The well known safety profile for lamivudine gives some reassurance. For zidovudine, the percentage of patients who experience adverse events such as gastrointestinal events (which are believed to be associated with plasma concentrations) may be increased. It is unlikely that haematological events (i.e anemia) would be increased as they are considered to be associated with overall exposure (AUC).

In general, lamivudine and zidovudine exposure in children are modestly higher than in adults. Lamivudine adult exposures (mean (CV%)) are Cmax: 1.22 ug/ml (24%), AUC0-24: 9.4 ug.h/ml

(27%) [EPV10001] and zidovudine adult exposures (mean (CV%)) are Cmax: 2.01 ug/ml (40%), AUC0-24: 4.8 ug.h/ml (29%) [NTZA1001].

Monte Carlo Simulations based on the revised population PK model were performed to predict zidovudine exposure for the proposed dosing regimens of scored Combivir. Results show that zidovudine AUC values simulated are consistent across the 3 weight-ranges and are consistent with the historical paediatric data (for the higher zidovudine dosing regimen i.e 160 mg/m²).
Cmax values are higher than the historical data and even more especially in the 21-30 kg weight-range as expected due to the inhomogeneous dosing regimen.

As Monte Carlo Simulation tended to predict higher zidovudine exposure, especially Cmax, PK data in paediatrics from study P53-04 and post-hoc model parameter estimates from PACTG 152 were re-analysed to predict zidovudine exposure (daily AUC and Cmax) from scored Combivir tablets.
When comparing predicted zidovudine exposure for the scored tablet from different methods, predicted zidovudine daily AUC for scored tablet by weight band are generally in agreement among the results from Monte Carlo Simulation, re-analysis of P53-04 (limited sample size), and PACTG 152. Predicted zidovudine Cmax for scored tablet by Monte Carlo Simulation are on average 41% and 10% higher than those from PACTG 152 in the weight group of 14-<21kg, and 21-<30kg, respectively.

When comparing predicted zidovudine exposure for the scored tablet to adults and paediatric data from currently approved zidovudine dosing regimens, predicted zidovudine daily AUC for scored tablet are higher than adult data from 300mg BID and paediatric data from 120mg/m² TID, but are similar to paediatric data from 160mg/m² BID.

Predicted zidovudine Cmax by Monte Carlo Simulation for the proposed scored tablet dosing regimens are on average 33% and 62% higher amongst children weighing 14-<21kg, and 21-<30kg, respectively, when compared to adults receiving 300mg BID. Predicted zidovudine Cmax for scored tablet by reanalysis of PACTG 152 are similar to adult and paediatric data from currently approved zidovudine regimens in the weight band of 14-<21kg, while predicted zidovudine Cmax in the 21-<30kg weight are 50% higher than adults and 86% higher than paediatric patients receiving 160mg/m² q8h.

It was noted that the MAH has initially submitted simulations in the group with unequal doses that did not reflect a 12 hours dose interval but rather was based on doses separated by 8 hours. The MAH has submitted simulations taking into account a dosing interval of 12 hours, which does not change the conclusions.

Proposed posology for Combivir:

Based on the results of simulations and taking into account the 2006 WHO recommendations, the MAH has proposed the following dosage recommendations for children over 14 kg:

Children weight	**Posology**
Children weighing **at least 30 kg**	One whole tablet twice daily
Children weighing **between 21 kg to 30 kg**	One half tablet in the morning One whole tablet in the evening
Children weighing **between 14 kg to 21 kg**	One half tablet twice daily

Discussion

All the results confirm that Cmax are higher and this is more relevant with the regimen half tablet AM/one tablet PM. Therefore, the main concern as regards the regimens proposed by the MAH is to determine whether or not the variations of plasma concentrations subsequent to the administration of inhomogeneous dosing for children weighing between 21 kg to 30 kg (i.e an half tablet in the morning and a whole tablet in the evening) could alter the safety and efficacy profiles of the drugs.
It is all the more critical that such an inhomogeneous dosing regimen is questionable specially taking into consideration the poor compliance to anti-HIV multitherapy.

Regarding Cmax values, the MAH recognised that there is a concern regarding the safety of the proposed dosing regimen. This concern must not be neglected, since the impact on the safety (and efficacy/adherence) of the scored tablets clearly depends on the type of adverse event. For example, an increase in vomiting can be assumed to have a greater impact than an increased incidence of nausea. However, it is known that gastrointestinal (GI) adverse events of zidovudine decrease over time. Therefore, the MAH was requested to carefully evaluate these events in a post-marketing study (e.g. in an observational cohort) and, if necessary, explore a regimen for diminishing these events (e.g. by either taking 3 x ½ tablet or by starting zidovudine therapy with the oral solution and switching to the tablet formulation after a few weeks). The MAH committed to submit a proactive pharmacovigilance survey and to submit a safety review focusing on Combivir paediatric scored tablets every 6 month. Within this variation the SPC is updated in order to warn prescribers for the possibly increased risk of adverse events. A respective statement on the possibility to change the dosing schedule in case of GI-intolerance by taking 3 x ½ tablet Combivir /day is inserted. Furthermore, results from Arrow study are expected. These issues are further discussed in the following safety and pharmacovigilance sections.

4.2 Clinical safety

No new safety data have been generated specifically with the scored tablets of Combivir.

Data on treatment with the combination of the components zidovudine/lamivudine in patients less than 12 years of age is provided by the randomised, doubleblind, study CNAA3006 (n=205). However, this study in children aged between six months and 13 years did not evaluate the new formulation of Combivir which is proposed in this current application, i.e. the tablets with a scored break line.
Study CNAA3006 compared Combivir + abacavir (n=102) to Combivir alone (n=103). Results show that less than 10% of participants in each arm experienced a treatment limiting adverse events (AE); nausea/ vomiting were the AE most frequently associated with Combivir + abacavir, were generally transient and did not lead to discontinuation of the study drug. Furthermore, incidences of grades 3 and 4 hepatic, haematologic, pancreatic, and renal toxicities occurred infrequently in both arms

In addition study APV29005, which investigated subjects aged 2 to 18 years receiving different dosing regimes of boosted and unboosted Fosamprenavir, once a day (QD) and twice a day (BID) dosing (Fosamprenavir BID, Fosamprenavir /Ritonavir BID, oral suspension or tablets) included seven subjects treated with zidovudine/lamivudine).

These studies did not suggest there is a difference in the adverse event profile of zidovudine/lamivudine in children under the age of 12 years compared with adolescents and adults.

5 Pharmacovigilance system

5.1 Risk Management Plan (RMP)

As an enlarged paediatric population will be exposed with this new formulation the CHMP requested the MAH to submit a RMP for Combivir scored tablets. The RMP should take into account the efficacy and safety concerns related to the use of Combivir in this new paediatric population, as detailed in this assessment report. Furthermore, the MAH should consider an educational program for prescribers and parents or caregivers to ensure that the dosing regimen should be applied as indicated.

The MAH has submitted a RMP and identified the following important potential risks with the use of Combivir paediatric scored tablet:
▪ Dosing recommendations resulting in over exposure
The pharmacokinetic population PK model that was used as the basis for the Monte Carlo simulations provides good predictions of AUC(0-24) values, however, Cmax values then tend to be biased to higher values. It is important to note that current dosing recommendations for paediatric patients result in higher exposures than exposures for adults.

▪ Inhomogeneous dosing regimen in children weighing 21 to 30 kg
In the pharmacokinetic population PK model, Cmax for both lamivudine and zidovudine were higher for the Half tab/Full tablet regimen, for the > 21 to 30 Kg weight group, compared to the homogenous TID regimen.
- about zidovudine safety, increased zidovudine Cmax may increase the percentage of patients who experience adverse effects such as gastrointestinal events, which are more generally believed to be associated with plasma concentrations; if gastrointestinal intolerance occurs, then a 0.5 tablet three times a day(TID) regimen with lower Cmax values may improve tolerability, however it is noted that this regimen would be less patient friendly; conversely, it is unlikely that zidovudine associated haematological events (e.g. anaemia) would increase as this is generally considered more associated with overall exposure (AUC).
- about zidovudine efficacy, the potential effect on efficacy and development of resistance is expected to be minimal if any, since phosphorylation steps would not be affected and taking into consideration the half-life for zidovudine-TP (~ 7 hours) which should be sufficient to maintain efficacious levels with minimal risk for the development of resistance. This is supported in part by a study which examined the short term viral load decline following monotherapy of zidovudine administered as 600 mg once daily versus 300 mg twice daily which demonstrated similar viral load declines over 14 days.
- about lamivudine safety, the increase in lamivudine AUC and Cmax is not considered to have clinical relevance with respect to adverse events, regarding results of the original dose ranging study in pediatrics that examined larger doses up to 10 mg/kg BID during 48 weeks; moreover, supportive data in the adult dose ranging trial, which examined doses from 0.25 mg/kg BID up to 10 mg/kg BID, showed similar adverse event profiles across all dose groups.
- about lamivudine efficacy, the half-life for the active lamivudine-TP is 16 hours, which should be sufficient to maintain efficacious levels, and this antiretrovial agent is currently approved for once daily dosing in adults. Since changes in phosphorylation are not observed with maturation, it is likely that the inhomogenous BID dosing will have similar efficacy to a "homogenous" twice daily.

▪ Risk of Choking Associated with Tablets in younger Children
There is a potential risk of choking (false route) associated with the half or whole scored tablets of Combivir in children < six years of age, although there are currently no data to indicate the likely level of this risk. Techniques and strategies have been developed to enable training of young children (<4 years or <20kg) to successfully swallow solid tablets and capsules. Therefore, children anticipated to be at risk of choking should either be properly trained to swallow the solid form or else prescribed the oral solution of lamivudine and zidovudine which has been specifically formulated for this population.

▪ Carcinogenicity in Children exposed to NRTIs
Preclinical studies with certain NRTIs have revealed some carcinogenic potential in rodents and transplacental carcinogenicity data are included in the EU SPC for Combivir. However current information from clinical studies and widespread clinical use has not revealed any clinical concerns: there is some limited data from longer-term follow up of children exposed in utero and neonatally to AZT (zidovudine) +/- lamivudine, who were enrolled in PACTG 219/076 or in the Women and Infants Transmission Study (WITS). No tumours of any kind were observed in exposed children.
The assessment of the risk for cancer in children exposed to antiretroviral medicinal products was considered not feasible to be performed within the planned MITOC study on mitochondrial toxicity in children exposed to NRTIs, but rather via linkage of HIV and cancer registries.

<u>Together to routine pharmacovigilance, additional pharmacovigilance activities are considered by the MAH:</u>
The ongoing paediatric trial, the **ARROW Study**, which is an independent investigator study, sponsored and co-ordinated by the Medical Research Council Clinical Trials Unit, London. The MAH is providing support in the form of antiviral drug supply, including scored solid forms of Combivir.
ARROW is a 5 year open-label randomised trial evaluating two strategic approaches for management of antiretroviral therapy in symptomatic HIV infected infants and children in Africa. Recruitment will take place over 18 months, with a maximum follow up of 5 years. 1200 children (6 months to 17 years old) will be enrolled from 4 sites in Africa (800 Uganda (3 sites), 400 Zimbabwe (1 site). Dosing of patients in ARROW is undertaken according to the weightbased dosing bands described in the WHO

2006 Infant and Children Treatment Guidelines and includes the 'inhomogeneous' whole tab/half tab dosing. Dosing for participants in ARROW is consistent with the dosing proposals described in the Type II variations for scored tablets of Epivir (lamivudine) and Combivir.
The ARROW study started recruitment in Uganda in March 2007 and in Zimbabwe in May 2007 and has already enrolled patients who are receiving scored tablets. The study ARROW may provide information regarding over exposure, dosing regimes and choking as adverse events will be reported and monitored.
Furthermore, the ARROW pharmacokinetic substudy is planned to address two distinct questions. Part I will evaluate the pharmacokinetics of the scored tablets of Combivir, Epivir and Ziagen, including switch from twice to once daily dosing where appropriate. Pharmacokinetics (PK) of Efavirenz (EFV) capsules or tablets once daily will also be measured. Part II will address an additional question regarding the switch from liquid to solid formulations in young children in resource-limited settings.

Upon CHMP request, the MAH committed to submit a proactive pharmacovigilance survey and to submit a safety review focusing on Combivir paediatric scored tablets every 6 month.

Risk minimisation plan
For important potential risks and missing information, routine risk minimisation activities are considered to be sufficient.
For inhomogeneous dosing regimen in children weighing 21 to 30 kg, the MAH is considering the usefulness of an educational program to prescribers and caregivers. Planned activities include consultation with paediatric experts and Key Opinion Leaders as well as careful consideration of the practical needs for implementation of any program.

A summary of the risk management plan for Combivir highlighting the safety concerns with lamivudine and zidovudine is presented below:

Summary of the EU Risk Management Plan

Safety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Dosing recommendations resulting in over exposure	Routine monitoring activities in place to identify reports of overdose, or adverse events associated with overdose	-
Inhomogeneous dosing regimen in children weighing 21 to 30 kg	Routine monitoring activities in place to identify reports of overdose, or adverse events associated with overdose	GSK is considering the usefulness of an education program to prescribers and caregivers
Risk of choking associated with tablets in younger children	GSK will monitor reports of choking in children to identify any new safety issue	-
Carcinogenicity in children exposed to NRTIs	Routine monitoring activities in place to identify reports of carcinogenicity. Regular review of medical literature, established networks with external experts and involvement with COHORTS	-

Further characterise safety profile in paediatrics post-marketing	Six-monthly post-marketing safety reviews (subject to review at the end of 2y to see if still required) on the paediatric data for the scored tablet. Explore feasibility of using observational cohorts and healthcare claims databases to assess real world use of CBV in paediatrics.	-
Further characterise safety profile in ARROW study	Explore the incidence of GI events within the ARROW study. Interim analyses of GI events from the ARROW study, yearly from Q2 2008	If applicable, explore a regimen for diminishing GI events

6 Overall discussion and benefit risk assessment

The CHMP considers that this new formulation is needed and welcomed. Indeed, the development of a scored tablet of Combivir answers a medical need insofar that fixed dose combinations are of particular interest for paediatric patients due to the well known problems in adherence to therapy in this target population. This is especially critical in view of the bad taste of the oral solutions available for the paediatric population.

The development of a scored tablet raised two critical difficulties; the switch of the zidovudine regimen from a three times a day to two times a day and the proposed inhomogeneous dosing regimen of Combivir.

The demonstration provided by the MAH for the switch of the zidovudine posology from a three times a day to a two times a day regimen relies on modelling with no new clinical data. Nevertheless, it has to be recognised that the twice daily regimen of zidovudine in paediatric patients is widely used in clinical practice and the recent WHO/PENTA support has reinforced such a use, as well as national guidelines.

In view of the data provided by the MAH, the zidovudine Cmax values obtained with the new proposed regimen with scored tablets are expected to be higher and the MAH recognised that there was a concern regarding the possible increased frequency of gastro-intestinal events. Therefore, the MAH was asked to give reassurance that the higher exposure of zidovudine by intake is unlikely to alter the safety profile of the drug in the target paediatric population.
In response to this concern the MAH committed to perform a proactive pharmacovigilance survey and to submit a safety review focusing on Combivir paediatric scored tablets every 6 month. If applicable, the MAH should systematically explore a regimen for diminishing these events (e.g. by either taking 3 times half tablet or by starting zidovudine therapy with the oral solution and switching to the tablet formulation after a few weeks). Within this variation the SPC is updated in order to warn prescribers for the possibly increased risk of adverse events. Furthermore, a statement on the possibility to change the dosing schedule in case of GI-intolerance by taking 3 half tablets of Combivir a day is inserted.
Moreover, the ARROW study is ongoing that is expected to further substantiate the PK and safety of Combivir scored tablet.

The MAH also committed to explore whether administration of crushed tablets with small amounts of semi-solid food or liquid is possible from a pharmaceutical quality point of view. This is proposed to be done within a follow-up measure to this variation.

Finally, the MAH committed to submit a type II variation for Retrovir to harmonise the posology with that of Combivir (i.e. change from a TID to a BID regimen).

Overall, given that this scored tablet is expected to simplify the use of this fixed combination in children, this type II variation is approvable taking into consideration the changes to the SPC, labelling and PL and the commitments to submit the above requested follow up measures and type II variation.

7 Changes to the product information

SPC
Section 3 "Pharmaceutical form"
Introduction of score tablets as requested by the MAH.

Section 4.1 "Therapeutic indication"
The CHMP agreed with the extension of indication to paediatric patients and replacement of film coated tablets by scored film coated tablets as requested by the MAH.
The approved indication is as follows:
"Combivir is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection (see section 4.2)."

Section 4.2 "Posology and method of administration"
The MAH proposed to revise section 4.2 to reflect the different dosing regimen based on children weight. This section was further updated upon CHMP request to include a statement informing that the dosing regimen for paediatric patients weighing 14-30 kg is based primarily on pharmacokinetic modelling and supported by data from clinical studies using the individual components lamivudine and zidovudine.
Since a pharmacokinetic overexposure of zidovudine can occur a statement was introduced to request a close safety monitoring is warranted in this group of patients. Furthermore, if gastrointestinal intolerance occurs in patients weighing 21 to 30 kg, an alternative dosing schedule with one-half tablet taken thrice daily can be applied in attempt to improve tolerability.
Combivir tablets should not be used for children weighing less than 14 kg, since doses can not be appropriately adjusted for the weight of the child.

Section 5.2 "Pharmacokinetic properties"
The MAH proposed to introduce a sentence on pharmacokinetics in children. This sentence is extracted from the Retrovir (zidovudine) SPC.
Following CHMP comments the MAH has revised this section to be in line with the section 4.2 CHMP.

The PL was updated accordingly.

The MAH took the opportunity of this variation to split the outer carton and bottle label.