

## Pharmacokinetics of two generic fixed-dose combinations for HIV-infected children (Pedimune Baby & Pedimune Junior) are similar to the branded products in healthy adults

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**Objectives:** Cipla Pharmaceuticals have developed generic fixed-dose combinations of stavudine, lamivudine and nevirapine for HIV-infected children (Pedimune Baby and Junior). We determined the pharmacokinetic profiles of stavudine, lamivudine and nevirapine in Pedimune and compared these with the branded products.

**Methods:** This Phase I, comparative, single-centre, open-label, three-period, single-dose study was designed as a pilot study to exclude large differences in pharmacokinetics. Six healthy males were randomized to the following regimen sequences: ABC; ACB; BCA; BAC; CAB; CBA (A = reference, B = Pedimune Baby, C = Pedimune Junior). Single doses of medication were administered at 3 time points 4 weeks apart. An 8 h pharmacokinetic curve was recorded at day 1 of every cycle after medication intake. In addition, blood samples were taken on days 2, 3, 4, 8 and 15.

**Results:** Non-parametric statistical tests revealed no statistically significant differences in  $C_{\max}$  ( $0.173 \leq P \leq 0.753$ ) and  $T_{\max}$  ( $0.317 \leq P \leq 1.000$ ) of stavudine, lamivudine and nevirapine between the two Pedimune formulations and the branded drugs. Also, there were no significant differences in  $AUC_{0-\infty}$  of stavudine, lamivudine and nevirapine between Pedimune Junior and the branded drugs ( $0.345 \leq P \leq 0.600$ ) and between Pedimune Baby and the branded drug for nevirapine ( $P = 0.463$ ). In contrast, the  $AUC_{0-\infty}$  of stavudine (mean change: +21%;  $P = 0.046$ ) and lamivudine (mean change: +14%;  $P = 0.028$ ) differed significantly between Pedimune Baby and the branded drugs, but these changes were considered not clinically significant.

**Conclusions:** The pharmacokinetic profiles of stavudine, lamivudine and nevirapine in Pedimune Baby and Junior are comparable to the branded products. Based on these results, it is acceptable to test the pharmacokinetics and dosing requirements of Pedimune in HIV-infected children.

Keywords: stavudine, lamivudine, nevirapine

### Introduction

In well-resourced countries, antiretroviral therapy (ART) with three or more potent drugs has resulted in major reductions in morbidity and mortality of HIV-infected adults and children.<sup>1,2</sup>

There are now intensive efforts by governments and non-governmental organizations to increase the number of people being treated with ART in resource-limited parts of the world where 90% of infected individuals live. For HIV-infected adults in these settings, pharmaceutical companies have reduced drug

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costs through separate pricing, and generic manufacturers have been allowed to produce ART combinations at lower costs without facing patent claims.

Cipla Pharmaceuticals is an India-based generic manufacturer that has produced a fixed-dose combination (FDC) tablet for HIV-infected adults (Triomune: 30 or 40 mg of stavudine, 150 mg of lamivudine and 200 mg of nevirapine), to be taken twice-daily without food restriction. Bioequivalence and clinical efficacy have been demonstrated.<sup>3–5</sup> At a price of less than 1 euro/day, Triomune is now a reasonable option for many adult patients, and is frequently used in access-to-care programmes.

In 2005, it was estimated that at least 660 000 children were in need of ART,<sup>6</sup> of whom 90% live in sub-Saharan Africa. However, fewer than 4% of individuals receiving ART in 2005 were children. There are several reasons for this including difficulties in making an early diagnosis of HIV in HIV-exposed infants and lack of personnel trained in paediatric ART management. However, arguably the biggest barrier is lack of appropriate formulations of ART, including FDC tablets, and simple dosing tables. Paediatric brand liquid formulations are expensive, may require water for reconstitution, which is not always available in good quality, and may require refrigeration, which is a particular problem in rural areas. Further, until recently, there were no FDC tablets for children. Triomune is sometimes prescribed dosed as half or quarter tablets. However, lack of scoring can result in inaccurate breaking and hence inaccurate dosing. Of more concern are preliminary data from a study in Malawian and Zambian children which showed that nevirapine underdosing was common, particularly in the youngest children receiving quarter tablets of Triomune.<sup>7</sup>

To address this issue, Cipla Pharmaceuticals have recently developed two generic fixed-dose combinations for HIV-infected children (Pedimune Baby and Pedimune Junior) including the same agents as in Triomune, but in a different dose ratio, with a higher dose of nevirapine. Pedimune Baby contains 6 mg of stavudine, 30 mg of lamivudine and 50 mg of nevirapine, while Pedimune Junior contains double the dose. Pedimune tablets are small, dispersible or crushable, and scored.

The primary objective of this pilot study was to determine the pharmacokinetic profile of stavudine, lamivudine and nevirapine in Pedimune Baby and Pedimune Junior after a single dose in healthy males, and to compare this with the individual branded products. The study was conducted in the Netherlands as a prelude to a pharmacokinetic study of Pedimune in HIV-infected children in Zambia, which was started recently.

## Materials and methods

This Phase I, comparative, single-centre, open-label, three-period, single-dose study was not designed as a bioequivalence study but as a pilot study to exclude large differences in pharmacokinetic profiles. Healthy male subjects aged 18–65 years were eligible for enrolment after pre-entry and laboratory evaluation. Subjects who tested positive for HIV and/or hepatitis B or C and subjects with abnormal clinical laboratory test results were excluded. Subjects were not allowed to take any concomitant drug (for 2 weeks preceding dosing), except for paracetamol and loperamide. The study protocol was reviewed and approved by the Ethics Committee of the Radboud University Medical Centre, Nijmegen, The Netherlands. Informed consent was obtained from all subjects before enrolment.

Subjects were randomized to one of the following regimen sequences: ABC; ACB; BCA; BAC; CAB; CBA.

Regimen A (reference): 24 mg of stavudine (24 mL of Zerit powder for suspension 1 mg/mL, Bristol-Myers Squibb), 120 mg of lamivudine (12 mL of Epivir solution 10 mg/mL, GlaxoSmithKline) and 200 mg of nevirapine (one Viramune tablet of 200 mg, Boehringer Ingelheim).

Regimen B (test 1): four combined-formulation tablets consisting of 6 mg of stavudine, 30 mg of lamivudine and 50 mg of nevirapine (Pedimune Baby, Cipla Pharmaceuticals).

Regimen C (test 2): two combined-formulation tablets consisting of 12 mg of stavudine, 60 mg of lamivudine and 100 mg of nevirapine (Pedimune Junior, Cipla Pharmaceuticals).

Single doses of medication, normalized to 200 mg of nevirapine, were administered at three time points 4 weeks apart. Medication was taken orally after a minimum fast of 3 h. One of the investigators directly observed medication ingestion. Breakfast and lunch were standardized on the day of medication ingestion and were administered 2 and 5 h after intake, respectively.

Blood was collected just before and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 24, 48, 72, 168 and 336 h after intake. Blood samples were stored at 2–8°C for a maximum of 8 h before being centrifuged. Immediately after centrifugation, plasma was separated and stored at –40°C until analysis. Plasma concentrations of stavudine and lamivudine were determined in all samples up to 24 h after intake by a validated HPLC assay with ultraviolet (UV) detection.<sup>8</sup> Plasma concentrations of nevirapine were determined in all samples by a validated HPLC assay with UV detection, modified from a method published by Hollanders *et al.*<sup>9</sup> The lower and upper limits of quantification for the modified assay were 0.03 and 15 mg/L, respectively. The intraday precision ranged from 0.4% to 11.4%, while additional variation as a result of performing the assay on different days ranged from 0.0% to 2.1%. The accuracy of the assay ranged from 100.1% to 104.8%.

The pharmacokinetic parameters  $C_{max}$  and  $T_{max}$  were calculated directly from observations of plasma concentrations. Non-compartmental pharmacokinetic analysis was performed by using the WinNonlin software package (version 4.1; Pharsight Corporation, Mountain View, CA, USA) to determine the pharmacokinetic parameter  $AUC_{0-\infty}$ .

Wilcoxon's signed rank test was used to compare  $C_{max}$ ,  $AUC_{0-\infty}$  and  $T_{max}$  between the generic and branded formulations. Descriptive statistics were carried out by using SPSS® software version 12.0 (SPSS Inc., 1989–2003).

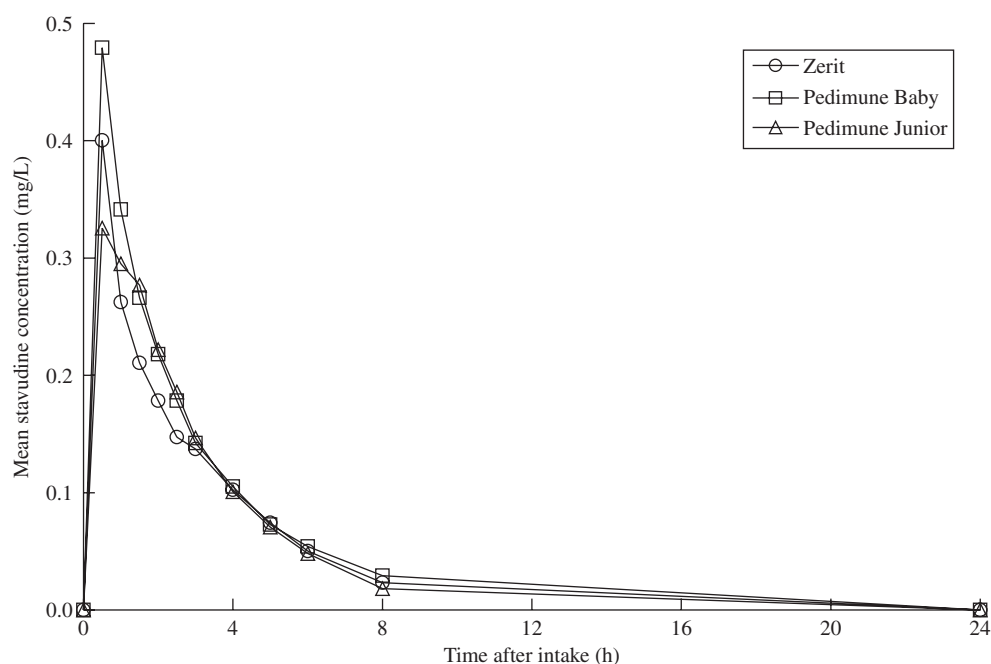
## Results

Six healthy white male subjects were enrolled in the protocol. The median age, height and body weight (range) were 43 (21–63) years, 1.84 (1.74–1.98) m and 86.5 (69.0–100.0) kg, respectively. All six males completed the study.

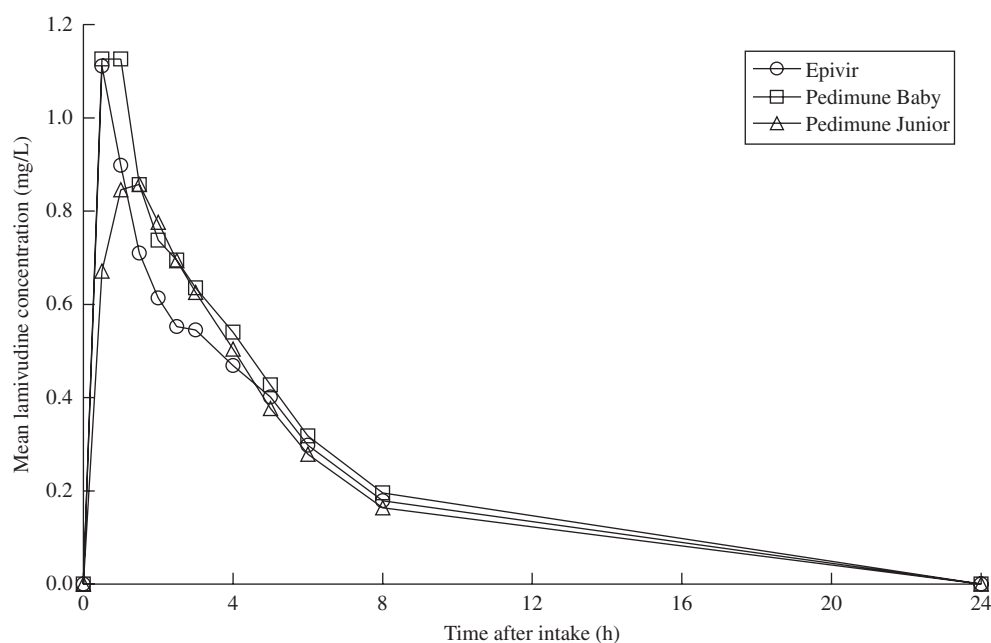
Plasma concentrations of stavudine, lamivudine and nevirapine after single doses of the branded drugs (A), Pedimune Baby (B) and Pedimune Junior (C) are illustrated in Figures 1–3, respectively. There are no large differences between the different plasma concentration–time curves.

Primary pharmacokinetic parameters of stavudine, lamivudine and nevirapine after single doses of the branded drugs (A), Pedimune Baby (B) and Pedimune Junior (C) are shown in Table 1.

Non-parametric statistical tests revealed no statistically significant differences in the  $C_{max}$  ( $0.173 \leq P \leq 0.753$ ) and



**Figure 1.** Mean stavudine concentrations (mg/L) in six healthy males after intake of a single dose of Zerit, Pedimune Baby and Pedimune Junior.



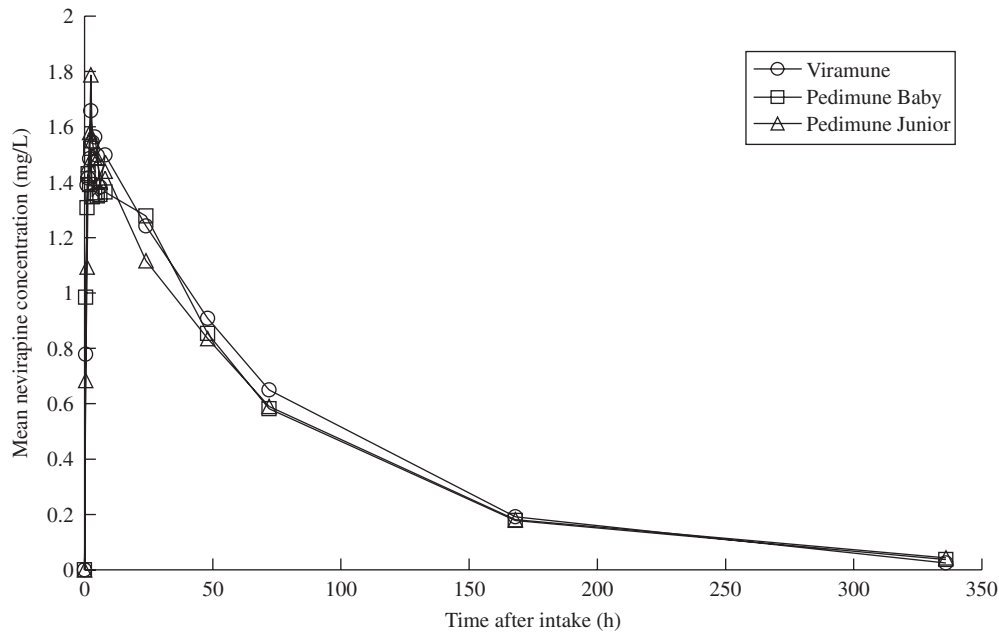
**Figure 2.** Mean lamivudine concentrations (mg/L) in six healthy males after intake of a single dose of Epivir, Pedimune Baby and Pedimune Junior.

$T_{max}$  ( $0.317 \leq P \leq 1.000$ ) of stavudine, lamivudine and nevirapine between the two Pedimune formulations and the branded drugs. Furthermore, no statistically significant differences in the  $AUC_{0-\infty}$  of stavudine, lamivudine and nevirapine were found between Pedimune Junior and the branded drugs ( $0.345 \leq P \leq 0.600$ ). The  $AUC_{0-\infty}$  of stavudine ( $P = 0.046$ ) and lamivudine ( $P = 0.028$ ) differed significantly between Pedimune Baby and the branded formulations, while there was no significant

difference in the  $AUC_{0-\infty}$  of nevirapine ( $P = 0.463$ ). For Pedimune Baby the mean  $AUC_{0-\infty}$  of stavudine and lamivudine was 21% and 14% higher compared with the branded drugs, respectively.

Treatments were generally well tolerated. No adverse events were reported after intake of Pedimune Junior. Reported mild adverse events, possibly related to treatment, were diarrhoea (1 out of 6 subjects on branded products and 1 out of 6 subjects

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**Figure 3.** Mean nevirapine concentrations (mg/L) in six healthy males after intake of a single dose of Viramune, Pedimune Baby and Pedimune Junior.

**Table 1.** Pharmacokinetic (PK) parameters of stavudine, lamivudine and nevirapine in six healthy males after intake of a single dose of branded drugs (Zerit, Epivir, Viramune), Pedimune Baby and Pedimune Junior

PK parameters	Branded drugs (A)	Pedimune Baby (B)	Pedimune Junior (C)
<b>Stavudine</b>			
$C_{max}$ (mg/L)	0.43 (0.19–0.54)	0.49 (0.26–0.77)	0.38 (0.29–0.52)
$AUC_{0-\infty}$ (mg·h/L)	1.05 (0.73–1.54)	1.27 (0.85–1.71)	1.08 (0.67–1.51)
$T_{max}$ (h)	1.08 (0.50–4.00)	0.58 (0.50–1.00)	0.83 (0.50–1.50)
<b>Lamivudine</b>			
$C_{max}$ (mg/L)	1.20 (0.55–1.56)	1.33 (0.70–1.92)	1.04 (0.83–1.24)
$AUC_{0-\infty}$ (mg·h/L)	4.48 (3.48–5.59)	5.09 (3.57–6.50)	4.41 (3.66–5.75)
$T_{max}$ (h)	1.25 (0.50–5.00)	1.00 (0.50–2.50)	1.67 (0.50–4.00)
<b>Nevirapine</b>			
$C_{max}$ (mg/L)	1.96 (1.64–2.29)	1.71 (0.96–2.91)	1.93 (1.48–2.48)
$AUC_{0-\infty}$ (mg·h/L)	136.05 (85.04–203.58)	127.92 (88.15–199.39)	127.53 (77.38–246.85)
$T_{max}$ (h)	2.33 (1.00–5.00)	6.25 (1.00–24.00)	2.42 (1.00–5.00)

Values are means (ranges).

on Pedimune Baby) and nausea (2 out of 6 subjects on branded products). All adverse events resolved spontaneously.

**Discussion**

This pilot study shows that the pharmacokinetic profiles of stavudine, lamivudine and nevirapine in Pedimune Baby and Junior are comparable to the individual branded products after intake of single doses.

A bioequivalence study is typically conducted as a single-dose, crossover trial. With three different formulations a minimum number of six subjects was needed for this pilot study to test all possible sequences. The study was not powered to prove bioequivalence, but to exclude large differences (>50%) in pharmacokinetic parameters.

Although the formulations are designed for HIV-infected children, it is generally not accepted to study pharmacokinetics of new agents or new formulations in healthy children. Therefore, healthy adults were included. Due to a possible effect of endogenous or exogenous oestrogenic hormones on the pharmacokinetics of nevirapine, the effect of nevirapine on oral contraceptives, more toxicity of nevirapine in healthy females, and the small sample size, we only included male subjects.

Non-parametric statistical tests revealed no statistically significant differences in the  $C_{max}$  and  $T_{max}$  of stavudine, lamivudine and nevirapine between the two Pedimune formulations and the branded drugs. Moreover, no statistically significant differences were found for the  $AUC_{0-\infty}$  of stavudine, lamivudine and nevirapine between Pedimune Junior and the branded drugs. While there was no significant difference in the  $AUC_{0-\infty}$  of

nevirapine between Pedimune Baby and Viramune, the  $AUC_{0-\infty}$  of stavudine and lamivudine was significantly higher (21% and 14%, respectively) after intake of Pedimune Baby when compared with the individual branded formulations. However, we do not consider these differences in  $AUC_{0-\infty}$  (far below 50%) to be large and find the pharmacokinetic profiles of stavudine, lamivudine and nevirapine in Pedimune Baby and Junior comparable to the individual branded products. In addition, it would be more worrisome if  $AUC_{0-\infty}$  of stavudine and/or lamivudine were lower instead of higher, as observed here. In general, virological failure is much more difficult to manage than toxicity.

Cipla Pharmaceuticals is currently conducting a formal bioequivalence study on Pedimune prior to applications for registration, and to meet prequalification criteria set by the WHO. Prior to results being available from this, we believe that the information from this independent pilot study showing comparable pharmacokinetic profiles of the three agents (stavudine, lamivudine and nevirapine) between the newly developed Pedimune tablets and the branded products, is sufficient for us to start a larger pharmacokinetic study in African HIV-infected children in Zambia who are a key target population for use of Pedimune. The children in our trial are closely monitored for potential toxicity and virological failure, because bioequivalence of the Pedimune tablets still needs to be proven. Given that large numbers of children are either receiving no ART, or inappropriate ART doses from part Triomune tablets, it is imperative that fixed-dose combinations of appropriate formulations and doses are tested urgently and then become available and licensed for children as soon as possible.

In conclusion, the pharmacokinetic profiles of stavudine, lamivudine and nevirapine in Pedimune Baby and Junior are comparable to the individual branded products. Based on the results of this pilot study, it is acceptable to start testing the pharmacokinetics and dosing requirements of Pedimune Baby and Junior in HIV-infected children, while monitoring closely for potential toxicity and virological failure.

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## Transparency declarations

None to declare.

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