

# Use and safety of fosamprenavir in HIV-infected children in the European Union: an ongoing post-marketing surveillance study

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## BACKGROUND

- Fosamprenavir (FPV) with low dose ritonavir (FPV/RTV BID) is licensed for HIV-infected children aged  $\geq 6$  years; the licensed paediatric dose is 18/3mg/kg FPV/RTV BID up to the adult regimen of 700/100mg BID
- In one paediatric clinical trial, neutropenia was reported more frequently than in adults
- The EMA requires Paediatric Investigation Plans (PIPs) to include development plans for medicines which include a long-term safety component
- We assessed the post-licensing use and safety of the licensed paediatric dose of FPV/RTV in HIV-1 infected children in the EU reported to cohorts participating in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC), for the European Medicines Agency (EMA)

## METHODS

- Four mother-child/ paediatric cohorts and a single centre cohort of children with parenteral (non-IDU) HIV transmission provided data to EPPICC, after gaining ethical approval
- Individual patient data were reported using the HICDEP data specification to the EPPICC data manager
- Children were considered to be on the licensed dose if their dose was within a window of  $\pm 20\%$  of the licensed dose or if they were on the adult dose
- Biochemistry tests reported included absolute neutrophil counts (ANC), total cholesterol (TC) and triglycerides (TG), and alanine transaminase (ALT)
- DAIDS gradings for paediatric adverse events (AEs) were used to identify severe or potentially life threatening events (grades 3/4); rates of AEs were calculated overall and by duration of time on FPV

## CHARACTERISTICS OF CHILDREN TAKING FPV

- 151 children in participating cohorts had ever taken FPV, of whom:
  - 110 had dosing and weight data (to calculate licensed dose)
  - 84 were on the licensed dose and aged 6-18 years at FPV start
- Characteristics of these 84 children are shown in Table 1

Table 1: Characteristics of children taking the FPV licensed dose

Characteristic	N or median	% or IQR
Cohort		
Belgium (Brussels)	24	29%
Italy	26	31%
Romania (Bucharest)	23	27%
Spain (Catalonia)	8	10%
UK & Ireland	3	4%
Male sex	43	51%
Age at start of ART (median yrs)	7	2-11
Age at start of FPV (median yrs)	15	12-17
Time on FPV (months)*	31	14-45
On FPV at last follow-up	47	56%

Notes:

\*For those on FPV at last follow-up, follow-up time has been censored at the last recorded visit date

- For the 37 children on the licensed dose who stopped taking FPV, main reasons for stopping were:
  - non-compliance/ patient decision (n=13)
  - immunological/ virological failure (n=11)
  - simplified treatment available (n=3)
  - GI tract toxicity (n=2)

## CONCLUSIONS AND NEXT STEPS

- Our study's findings suggest that the rate of severe or potentially life threatening adverse events was low, and that there was no discernible trend by duration of exposure to FPV. Thus findings indicate no apparent safety concerns regarding the current licensed dose of FPV
- Even when grade 3/4 events did occur, it would be difficult to attribute them specifically to FPV, given that other ART drugs would have been prescribed concurrently
- Findings also suggest that FPV is relatively infrequently prescribed to children living in the EU
- We plan to expand this study so that it is used as a pharmacovigilance model for other ART drug in future years. We will then be able to compare rates of adverse events between different drugs, strengthening the scientific aspects of the work
- However due to lack of standardisation of data sets between cohorts, many cohorts had to go back to participating clinics to collect additional data specifically for this study; this activity needs adequate resourcing
- With further improvements in data quality in future years, this study demonstrates the feasibility of using cohort studies to provide long-term safety data for ART drugs. This is important as these data are often not available from any other source

## RATES OF ADVERSE EVENTS

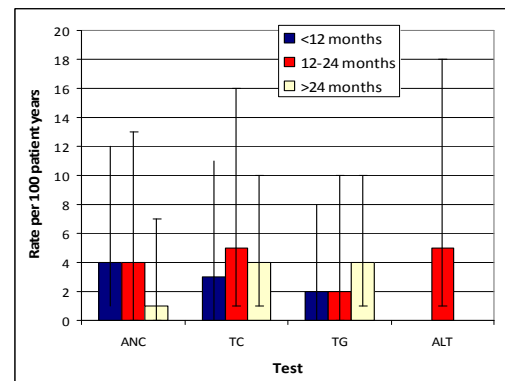
- Table 2 shows the number of patients experiencing a grade  $\geq 3$  event, the number of  $\geq 3$  events, and the overall AE rate per 100 person years for ANC, TC, TG and ALT, for 75 children for whom biochemistry data were available

Table 2: Rates of grade 3/4 adverse events by laboratory marker

Test	No. patients grade $\geq 3$	No. events grade $\geq 3$	Rate of events per 100 person yrs (95% CI)
ANC	5	6	3 (1-6)
TC	2	8	4 (2-8)
TG	2	5	2 (1-6)
ALT	1	2	1 (0-5)

- Figure 1 summarises rates of adverse events for ANC, TC, TG and ALT by duration of time taking FPV

Figure 1: Rates (95% CIs) of grade 3/4 adverse events for selected lab markers by duration of time taking the FPV licensed dose



- In general, the number and rate of grade 3/4 events was low, although confidence intervals were wide due to sparse data
- Of the 10 patients in total who experienced a grade 3/4 event, only 1 was known to have had a similar event in the 12 months prior to starting FPV

## COLLABORATORS AND FUNDING

### EPPICC contributing cohorts:

Belgium:	Hospital St Pierre Cohort, Brussels (Tessa Goetghebuer)
Italy:	Italian Register for HIV infection in children (Maurizio de Martino, Luisa Galli)
Spain:	CORISPE-cat (Antoni Noguera-Julian) Madrid Cohort of HIV-infected Children (Jose Thomas Ramos Amador)
Romania:	"Victor Babes" Hospital Cohort, Romania (Dan Duiculescu, Luminita Ene)
UK & Ireland:	National Study of HIV in Pregnancy and Childhood (Pat Tookey) Collaborative HIV Paediatric Study (Ali Judd, Di Gibb)

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