



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

## Reyataz

(atazanavir sulfate)

Procedure No. EMEA/H/C/000494/P46 74.4

CHMP assessment report for paediatric use studies  
submitted according to Article 46 of the Regulation (EC)  
No 1901/2006

**Assessment Report as adopted by the CHMP with  
all information of a commercially confidential nature deleted**



# 1. assessment

## 1.1. Introduction

This report covers the final report from the study AI424-450 "Pharmacovigilance study to define the long-term safety profile of atazanavir/ritonavir in HIV-1-infected children and adolescents in Europe" as following post-authorisation commitments undertaken by the MAH.

The Marketing Authorization Application (MAA) in the EU for Reyataz (atazanavir) was approved on 2-Mar-2004. At first, atazanavir was indicated in combination with ritonavir for the treatment of HIV-1 infected adults in combination with other antiretroviral products. Then, in 2010 an extension of indication for atazanavir was accepted (variation II-57) to include HIV-1 infected paediatric patients 6 years of age and older to be used in combination with other antiretroviral medicinal products. At that time, the CHMP has highlighted the need for a post marketing surveillance program to further characterize the safety profile of atazanavir in children and adolescents.

The MAH submitted in May 2010 an observational study protocol (AI424P49) untitled "Post Marketing safety surveillance program in HIV-infected children exposed to atazanavir in Europe" which was assessed by the CHMP in March 2011

The MAH has provided the first interim analysis of the pharmacovigilance study to define the long-term safety profile of atazanavir (ATV) in HIV-1-infected children and adolescents in Europe (AI424-450) reported to European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) in 2012 and the second one in 2013.

In the current assessment report the *final* report dated July 2014 is assessed.

## 2. Scientific discussion

### 2.1. Introduction

Reyataz® contains the active substance atazanavir (ATV), which is a potent human immunodeficiency virus (HIV-1) protease inhibitor (PI) indicated in combination with other antiretroviral medicinal products and low dose ritonavir (rtv), for the treatment of HIV infection in adults and paediatric patients 6 years of age and older. Very limited data are available from children aged 6 to less than 18 years.

The MAH contracted the PENTA Foundation/ European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) to conduct a pharmacovigilance study of the use and safety of ATV in children in the European Union.

The primary objective of the study was:

- To monitor adverse events in HIV-infected children < 18 years old who are exposed to ATV in a real-world setting

The secondary objectives were:

- To describe the pattern of use of ATV in HIV-infected children < 18 years old
- To describe off-label use of ATV/rtv in paediatric patients (excluding in utero exposure)

## 2.2. Methodology

Eleven mother-child and/ or paediatric cohorts who participate in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) provided data for this study. Each cohort reported individual patient data for all paediatric patients in their studies who had ever received ATV as part of an antiretroviral therapy (ART) regimen on or after 1 January 2011.

Data collected included demographics, deaths and losses to follow-up, as well as follow-up data (both pre- and post-ATV) for patient i.e weights, ART, AIDS events, CD4 and HIV-1 RNA, key haematology and biochemistry results, and adverse events.

The inclusion criteria for this study were as follows:

- HIV-infected paediatric patients aged <18 years;
- exposed to ATV on 1 January 2011 or started taking ATV after this date.

Data on demographic characteristics, ART treatment and adverse events occurring while on ATV were displayed and analysed separately for patients who initiated ATV in accordance to the recommended dose for weight, age and RTV co-administration (on-label) and those who did not. A total of 6 groups have been defined as follows:

- On-label use:
  - (i) 6-<18 years taking the licensed dose of ATV/r (or within a window of +/- 20% of the licenced dose) i.e. for 15-<20kg 150mg ATV, 100mg RTV, for 20-<40kg 200mg ATV, 100mg RTV and for ≥40kg 300 mg ATV, 100mg RTV,
  - (ii) 6-<18 years, weight ≥40kg taking 400mg ATV/r q.d. then 300mg ATV/r q.d.
- Off-label use
  - (iii) 6-<18 years, weight ≥40kg, taking 400mg or 300mg ATV q.d. unboosted,
  - (iv) 6-<18 years, taking any other unlicensed ATV dose,
  - (v) <6 years taking boosted or unboosted ATV with weight and dose measurements,
- Missing data
  - (vi) <18 years, with missing weight or dose (only demographic characteristics and ART treatment are presented for this group since interpretation of the results is limited without weight and dose information).

Prior to EMA licensing of ATV in paediatrics, European paediatric guidelines suggested a dose of 400mg ATV with 100mg RTV in children from 4 years of age. The majority of patients on 400mg ATV/r switched to a dose of 300mg ATV/r following its licensing, hence the rationale for group.

Due to the large proportion of children from the UK/Irish cohort, laboratory adverse event data have been analysed separately for this cohort and clinical adverse data are presented by country.

Children are considered to have missing weight if there was no weight recorded within the 3 months prior to or following the start date of ATV. A dose was considered missing if no dose was recorded on the start date of ATV.

Division of AIDS (DAIDS) gradings for paediatric adverse events were used to categorise the severity of laboratory adverse event data.

The number of patient, laboratory tests and severity of events are reported in 4 distinct time periods: (a) 12-months pre-ATV initiation (prior to start ATV); (b) 0-<12months since initiation of ATV; (c) 12-24 months after initiation of ATV; and (d) >24 months after initiation of ATV. Rates of first events are reported in each of the four time periods

after start of ATV per 100 person years (PY) for patients on the licensed dose (group i) only if there were  $\geq 20$  patients during the time period. Rates were not calculated for the other dosing groups due to small sample sizes or for the 12-months period pre-ATV due to the complex ART treatment histories of many patients starting ATV.

### **2.3. Data review**

#### **Results**

Data are presented for all paediatric patients who took ATV on or after 1 January 2011 and were reported to an EPPICC cohort up to February 2014 (last patient last visit date was 2/02/2014).

The cohorts participating in this final report analysis are:

-the 6 participating cohorts initially planned per protocol:

- UK/Ireland Collaborative HIV Paediatric Study (CHIPS) and National Study of HIV in Pregnancy and Childhood (NSHPC)
- CoRISPE-cat, Catalonia, Spain (formerly NENEXP project)
- Hospital St Pierre Cohort, Brussels, Belgium
- Italian Register for HIV Infection in Children, Italy
- CoRISPE-1, Spain (now including the Madrid Paediatric Cohort study)
- Karolinska University Hospital, Stockholm, Sweden
- The Swiss Mother and Child HIV cohort study (MoCHiV)

-the 4 following participating cohorts not originally planned per protocol which finally participated in this final report:

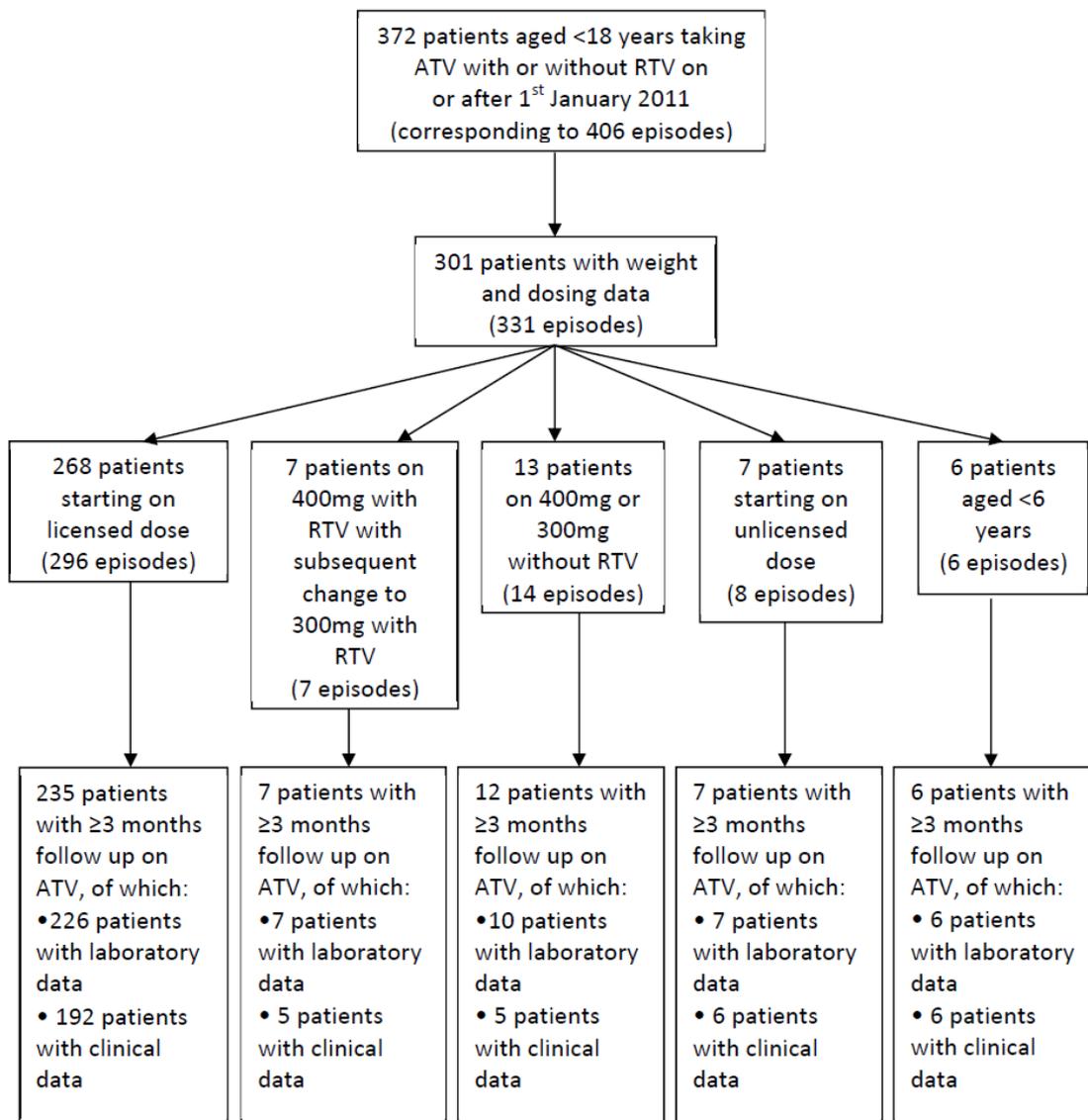
- Copenhagen Cohort, Denmark
- Centro Hospitalar do Porto, Portugal
- The Republican Hospital for Infectious Disease, St Petersburg, Russia,
- Thailand Program for HIV prevention and treatment (PHPT) Study Group, Thailand.

-the 3 non-participating cohorts which were originally planned per protocol are:

- the German Competence Network, which had no eligible patients,
- the European Collaborative Study, which had no eligible patients,
- Victor Babes Hospital Cohort, Bucharest, Romania, which had no eligible patients.

Cumulatively the 11 cohorts from 10 countries provided data on 372 patients who had ever taken any dose of ATV since 1<sup>st</sup> January 2011. See figure 1 below

Figure 1: Flowchart of patients and first episodes\* on ATV



Note: \*Patients may have multiple time periods on an ATV containing regimens, which are referred to as episodes. Here the classification of the dosing group is based on the age, weight, dose and co-administration of RTV at the start of their first episode on ATV.

In the group (vi) "missing weight or dose", there are 71 patients aged <18 years with missing weight or dose (n=61 had ≥3 months of follow-up).

#### 2.4. Characteristics of patient taking ATV

Out of 372 patients taking ATV since 2011, 44% of patients were male, 54% were black African, and almost all (95%) were infected with HIV through mother to child transmission. A total of 108 (29%) had been diagnosed with AIDS, 4 patients were co-infected with hepatitis C and 5 with hepatitis B. And 3 patients died during the follow up time. Most patients included came from the UK/Irish cohort (n=210, 56%), then from the 2 Spanish cohorts (n=52, 14%) then from the Danish cohort (n=41, 11%).

Characteristics of all patients taking ATV (n=372) are summarized in the table 1 below:

	Aged 6-<18 years on licensed dose (n=268)	Aged 6-<18 years on 400mg q.d. then 300mg q.d. + RTV (n=7)	Aged 6-<18 years on 400mg or 300mg q.d. unboosted (n=13)	Aged 6-<18 years only ever on other unlicensed dose (n=7)	Age <6 years (n=6)	Missing weight or dose (n=71)	Total (n=372)
	n (column %)						
<b>Cohort</b>							
Belgium	17 (6)	0 (0)	3 (23)	1 (14)	0 (0)	2 (3)	23 (6)
Denmark	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (4)	3 (1)
Italy	9 (3)	1 (14)	0 (0)	0 (0)	1 (17)	30 (42)	41 (11)
Portugal	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (3)	2 (1)
Russia	5 (2)	0 (0)	3 (23)	0 (0)	0 (0)	0 (0)	8 (2)
Spain <sup>1</sup>	38 (14)	0 (0)	4 (31)	0 (0)	2 (33)	8 (11)	52 (14)
Sweden	10 (4)	1 (14)	0 (0)	0 (0)	0 (0)	1 (1)	12 (3)
Switzerland	5 (2)	0 (0)	0 (0)	0 (0)	0 (0)	3 (4)	8 (2)
Thailand	12 (4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	13 (3)
UK/Ireland	172 (64)	5 (71)	3 (23)	6 (86)	3 (50)	21 (30)	210 (56)
<b>Gender</b>							
Male	121 (45)	3 (43)	6 (46)	1 (14)	3 (50)	28 (39)	162 (44)
<b>Ethnic group</b>							
White	39 (15)	0 (0)	6 (46)	0 (0)	1 (17)	11 (15)	57 (15)
Black African	163 (61)	6 (86)	6 (46)	5 (71)	2 (33)	20 (28)	202 (54)
Other	55 (21)	0 (0)	1 (8)	2 (29)	2 (33)	8 (11)	68 (18)
Unknown	11 (4)	1 (14)	0 (0)	0 (0)	1 (17)	32 (45)	45 (12)
<b>Mode of infection</b>							
MTCT	255 (95)	7 (100)	13 (100)	7 (100)	6 (100)	67 (94)	355 (95)
Other	5 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	6 (2)
Unknown	8 (3)	0 (0)	0 (0)	0 (0)	0 (0)	3 (4)	11 (3)
HCV positive (antibody or PCR)	1 (0)	0 (0)	1 (8)	0 (0)	0 (0)	2 (3)	4 (1)
HBV positive (surface antigen)	3 (1)	0 (0)	2 (15)	0 (0)	0 (0)	0 (0)	5 (1)
Ever AIDS event during follow-up	82 (31)	2 (29)	3 (23)	3 (43)	3 (50)	15 (21)	108 (29)
Died during follow-up	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	3 (1)

Notes

<sup>1</sup>Patients from the three paediatric cohorts in Spain (Madrid, CoRISPE-1 and CoRISPE-cat) are presented together here.

Among the off-label use patients, there were 13 patients on unboosted ATV 400mg or 300mg q.d. doses, 3 came from the Belgian cohort, 4 from the Spanish cohorts, 3 from the Russian cohort and 3 from the UK/Ireland; 3 had an AIDS diagnosis. For the 7 patients starting ATV on an unlicensed dose, 6 were from the UK/Irish cohort and one from the Belgian cohort; 3 had ever been diagnosed with AIDS. Among these 7 patients, 3 received an unlicensed dose for weight, 1 patient took twice daily dosing and the other 3 continued to take 400mg per day without reverting to 300mg dose. Six patients <6 years of age took ATV, 3 from UK/Ireland, 2 from Spain and 1 from Italy; 3 had a previous AIDS diagnosis.

The **table 2** presents ART-related characteristics of patients when starting a ATV-containing regimen, as well as during subsequent follow-up.

Within the licensed dose group, the median age at the start of any ART regimen was 4.4 years (IQR 1.1-9.4 years) which was similar to the median across all six groups (median 4.3 years, IQR 1.1-9 years). The median age at start of an ATV-containing regimen in this group was 13.5 years (IQR 11.5-15 years), the median duration of ART exposure prior to start of ATV-containing regimen was 7.9 years and only 25 (9%) were ART naïve when they started ATV. At the start of ATV, over half (54%) of patients in the licensed dose group had a viral load ≤400 copies/mL documented (although for 37 patients a viral load measurement within 3 months following ATV start was missing) and the median CD4 count at ATV start was 512 cells/mm<sup>3</sup> (IQR 349-796).

The median time on an ATV-containing regimen (by discontinuation of ATV, or by last follow-up for those who remained on ATV) was 22 months for the licensed dose group and 59 months for those taking 400mg ATV/r q.d. then 300mg ATV/r q.d. regimens. Among the off-label groups, the characteristics of patients were broadly similar to the on-label groups except for children aged <6 years group, who had a median age of 1.8 years at start of any ART regimen, with higher median viral load at start of ATV and shorter median duration on ATV (20 months vs 40 and 46 in the unboosted and unlicensed dose group respectively).

**Table 2 Antiretroviral therapy profile of all paediatric patients taking ATV (n=372)**

	Treatment status (n (%) or Median [95% CI])						Total (n=372)
	Aged 6-<18 years on licensed dose (n=268)	Aged 6-<18 years 400mg q.d. then 300mg q.d. + RTV (n=7)	Aged 6-<18 years on 400mg or 300mg q.d. unboosted (n=13)	Aged 6-<18 years only ever on other unlicensed dose (n=7)	Age <6 years (n=6)	Missing weight or dose (n=71)	
Age starting ART (years of age)							
Median age at ART start <sup>1</sup>	4.4 [1.1,9.4]	5.6 [2.5,8.5]	3.7 [0.7,12.3]	5.7 [2.6,8.2]	1.8 [0.6,3]	4.2 [1.8,4]	4.3 [1.1,9]
Age starting ATV (years of age)							
<6 years	0 (0)	0 (0)	0 (0)	0 (0)	6 (100)	0 (0)	6 (2)
6-8 years	21 (8)	0 (0)	0 (0)	0 (0)	0 (0)	2 (3)	23 (6)
9-11 years	69 (26)	2 (29)	3 (23)	4 (57)	0 (0)	17 (24)	95 (26)
12-14 years	111 (41)	2 (29)	4 (31)	3 (43)	0 (0)	25 (35)	145 (39)
15-<18 years	67 (25)	3 (43)	6 (46)	0 (0)	0 (0)	27 (38)	103 (28)
Median age at ATV start	13.5 [11.5,15]	13.7 [11.5,15.9]	14 [12.4,16.1]	12 [11.4,13.2]	4.9 [3.7,5.5]	14.4 [11.8,15.6]	13.5 [11.4,15.2]
Duration on ART before ATV (years)							
<2 years	48 (18)	0 (0)	3 (23)	0 (0)	2 (33)	8 (11)	61 (16)
2-4 years	37 (14)	1 (14)	1 (8)	1 (14)	2 (33)	11 (15)	53 (14)
5-9 years	89 (33)	4 (57)	4 (31)	5 (71)	2 (33)	17 (24)	121 (33)
>=10 years	94 (35)	2 (29)	5 (38)	1 (14)	0 (0)	35 (49)	137 (37)
Median duration	7.9 [3.5,11.2]	9 [5.2,11.7]	9.4 [4.2,12.1]	6.3 [5.2,7.6]	2.8 [0.5,2]	9.5 [4.2,12.3]	7.9 [3.6,11.4]
ART history before ATV							
Naive	25 (9)	0 (0)	2 (15)	0 (0)	2 (33)	5 (7)	34 (9)
1-7 ART drugs	106 (40)	2 (29)	5 (38)	4 (57)	4 (67)	27 (38)	148 (40)
8+ ART drugs	137 (51)	5 (71)	6 (46)	3 (43)	0 (0)	39 (55)	190 (51)
VL at ATV start							
<=400 c/ml	146 (54)	5 (71)	7 (54)	2 (29)	1 (17)	30 (42)	191 (51)
>400 c/ml	85 (32)	1 (14)	2 (15)	3 (43)	4 (67)	11 (15)	106 (28)
Missing	37 (14)	1 (14)	4 (31)	2 (29)	1 (17)	30 (42)	75 (20)
Median VL (log <sub>10</sub> c/ml)	2.1 [1.6,3.4]	2 [1.6,2.5]	1.7 [1.7,1.7]	4 [1.6,4.1]	5 [4.9,5]	1.7 [1.6,2.6]	2 [1.6,3.4]
CD4 at ATV start							
Value present	216 (81)	6 (86)	8 (62)	5 (71)	5 (83)	41 (58)	281 (76)
Missing	52 (19)	1 (14)	5 (38)	2 (29)	1 (17)	30 (42)	91 (24)
Median CD4 count (c/mm3)	512 [349,796]	623.5 [193,914]	572.5 [408,965]	360 [226,490]	693 [593,737]	588 [437,824]	534 [354,799]
CD4% at ATV start		29					
Value present	204 (76)	6 (86)	8 (62)	5 (71)	5 (83)	36 (51)	264 (71)
Missing	64 (24)	1 (14)	5 (38)	2 (29)	1 (17)	35 (49)	108 (29)
Median CD4%	25 [17,33]	29 [16,32]	32 [26,35]	20 [16,21]	32 [25,33]	29 [23,38]	25.1 [18,34]
Time on ATV							
Median time on ATV (months) <sup>2</sup>	21.7 [9,39]	58.6 [31,64]	40 [15,59]	45.5 [13,50]	20.2 [12,31]	23.5 [11,44]	22.8 [10,42]

Notes

1 Excludes ART for pMTCT

2 For those still on ATV at last follow-up, follow-up has been censored at the last recorded visit date.

## Laboratory results

Among the 235 patients aged 6-<18 years on the licensed dose who had ≥3 months of follow-up, laboratory data were available for 226/235 patients:

-for ANC test results available for 193 patients (1653 ANC test results), 8 patients had at least one grade 3 or 4 event on ATV with the rate being highest 12-24 months after starting ATV leading to an incidence rate of first events of 4 per 100 PY (95% CI 1-10),

-for total cholesterol results available for 217 patients, only one patient had a grade 3 or 4 event while on ATV, which occurred <12 months after ATV start and 60 patients had at least one grade 2 event whilst on ATV; the incidence rate was 30 per 100 PY both <12 months and 12-24 months after starting on ATV (95% CI 22-41 and 95% CI 20-42 respectively).

-for triglyceride (TG) test results reported in 211 patients (1186 results), there have been one grade 3 or 4 event reported after >24 months on ATV.

-for alanine transaminase (ALT) test results reported for 187 individual patients (1528 test results overall), four patients had grade ≥3 events; 3 during the first 12 months on ATV and 1 after >24 months on ATV.

-a total of 1407 bilirubin (BIL) test results were available for 188 patients : 92 patients (49% of those with tests available) had at least one grade 3 or 4 test result, giving an overall incidence of 29 events per 100 PY (95% CI 23-35). For BIL events, the incidence rate was highest in the first 12 months on ATV at 66 per 100 PY (95% CI 52-84) falling to 53 per 100 PY (95% CI 39-70) 12-24 months after ATV start and 32 per 100 PY (95% CI 23-44) after >24 months. Similarly, incidence rates of grade 2 BIL events were highest in the first 12 months of ATV use (102 per 100 PY, 95% CI 83-125) and declined but were sustained thereafter (e.g. 38 per 100 PY, 95% CI 28-51 after > 24 months).

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-none of the 66 patients tested for fasting plasma glucose (FPG) had a grade $\geq$ 3 result, while one of 48 patients tested for non-fasting plasma glucose (non-FPG) had a grade $\geq$ 3 event.

-for pancreatic amylase tests (P-AMY) reported in 74 patients (441 tests overall), 4 patients had a grade  $\geq$ 3 result all within 12 months and 2 again during 12-24 months after starting ATV. Out of the 52 patients tested for lipase (LIP), one had a grade 3 or 4 event.

Among the 7 patients aged 6-<18 years on 400mg q.d. then 300mg q.d ATV with RTV, all 7 patients tested for BIL had at least 1 grade 3 or 4 event. All continued on ATV and four patients had a subsequent normal BIL result.

In the off-label use groups, among patients on 400mg q.d. or 300mg unboosted dose, 10 patients had laboratory data: one patient had a grade 3 or 4 ANC event, 4 patients had grade $\geq$ 3 BIL results and 1 patient had grade $\geq$ 3 P-AMY results. Six of the 7 patients starting ATV on an unlicensed dose were from the UK/Ireland cohort.

In general, the numbers and rates of grade $\geq$ 3 events across all dosing groups were low. However, rates of grade 3 and 4 (and indeed 2) hyperbilirubinaemia were high and sustained although anecdotally clinicians reported that children remained well despite hyperbilirubinaemia, generally continued on an ATV-containing regimen and only stopped taking ATV if the parent or child was concerned that the child a yellow pallor.

### **Adverse events**

#### Adverse events reported as related to ATV

Clinical data were available for 80% (n=214) of the 267 patients with weight and dosing data and  $\geq$  3 months of follow-up.

In the 235 children on the licensed dose of ATV and with  $\geq$ 3 months of follow-up (group i), 192 had clinical data available of which 26 had clinical adverse events considered as at least possibly causally related to ATV :

-20 patients experienced hyperbilirubinaemia of which none was life-threatening but one was considered as serious,

-1 patient experienced symptomatic hepatitis with jaundice considered as non-serious and another patient had "hepatic disease" reported, both have been considered as possibly related to ATV,

-3 other SAEs were reported: one proteinurea, one rash and one lipodystrophy,

-other non-serious events were reported, one case of diarrhea and one including "nausea, vomiting and respiratory disorders".

Among the 5 patients in the 400mg ATV/r q.d. then 300mg ATV/r q.d. dosing group who had clinical data available, one patient had 2 non-serious adverse events considered as related to ATV, hyperbilirubinaemia and elevated CK. The patient continued ATV.

Among patients in the off-label groups and with clinical data available, there have been no clinical adverse events reported in the 5 patients on unboosted ATV, the 6 patients on an unlicensed dose and in the 6 children aged <6 years.

#### SAEs reported by the clinician as unlikely to be or not causally related to ATV or where the causal association with ATV was not designed or was reported as unknown

SAE were reported for 9 patients, all of whom were in the licensed dose group.

Two SAEs were reported as not causally related to ATV: a case of suspected meningitis and a patient undergoing an operation. Both patients continued ATV.

Among the 7 patients with SAEs whose causality was not designated or reported as unknown, 4 patients had hyperbilirubinaemia and one patient had raised triglycerides. Of the 5, 4 discontinued ATV for unrelated reasons and 3 subsequently re-started ATV. The remaining 2 patients died: one from Belgium died of a non-AIDS defining cancer and the other from Thailand following diagnosis of multiple SAEs (PCP, anaemia, cryptococcal meningitis and hypokalaemia) over an 8 month period. Both deaths occurred more than 18 months after ATV discontinuation and the reason was not provided for the patient from Belgium and reported as virological failure for the patient from Thailand.

Among patients with missing weight or dose, there was one death in a patient who had started ATV when ART-naïve aged 13 years and with a weight of 28 kg and CD4 cell count of 37 cells/mm<sup>3</sup>. The patient died 14 months later while on ATV+RAL+3TC+ddI (unboosted) regimen. The patient experienced multiple AIDS-defining conditions including Mycobacterium genevense systemic infection, wasting syndrome, Kaposi's sarcoma and liver failure. The death was attributed by the clinician to wasting syndrome.

Assessor's comments:

Overall there have been 5 serious and 24 non-serious adverse events reported in 27 patients that were considered to be causally related to atazanavir. The serious adverse events considered as at least possibly related are 1 rash with hyperbilirubinaemia (patient still on ATV, outcome unknown), 1 lipodystrophy (patient still on ATV but event resolved several months after), 1 proteinuria (patient still on drug, outcome unknown) and 1 "hepatic disease" reported the same day ATV was started which led to discontinue ATV and event resolved .

These ADRs reported which are mainly hyperbilirubinaemia constitute listed adverse events.

The 3 deaths reported in patients receiving ATV-containing regimen can be attributable to the underlying infectious disease.

Laboratory abnormalities reported which are mainly hyperbilirubinemia, are listed .

The number of children receiving ATV-containing cART is still low to draw firm conclusions. The available data indicate that the safety profile, based on the review of ADRs reported in pediatric patients receiving ATV-containing cART, is not different from that of the adult patients.

### Discontinuations

A total of 71 of the 372 patients (19%) discontinued ATV at the time of their last follow-up visit.

Of the 268 patients in the licensed dose group, 19% (n=50) discontinued ATV, 8% within the first month, 30% at 1-<6 months after starting ATV, 14% at 6-<12 months and 48% after ≥12 months on the drug. The reasons provided were: treatment failure(9), toxicity (8), more effective treatment available(1), non-compliance (6), patient's wishes (5), unspecified side effects (6), treatment simplification (5), structured treatment interruption (1), physician's decision(1) and unknown (8). For patients who discontinued ATV more than once, reasons for discontinuation are reported for the final episode only.

None of the 7 patients on the 400mg ATV/r q.d. then 300mg ATV/r q.d. dose had discontinued ATV by last follow-up.

Among the patients in the off-label groups, 4(31%) of the 13 patients in the unboosted dose group discontinued ATV due to: treatment failure (1), patient's wishes (2), and treatment simplification (1).

Similarly, in the group taking any other unlicensed ATV dose, 2(29%) of the 7 patients discontinued ATV due to: patient's wishes (1) and pregnancy (1). Two of the 6 patients in the <6 years group discontinued ATV both due to treatment failure.

**Assessor's comment:**

The review of reasons for discontinuation also did not reveal new safety information. Finally, no new safety issues have been identified.

**Context data**

The MAH provided context data, i.e. characterisation of cohorts participating to this study (e.g. not only patients on ATV-containing CART therapy but any cART). The UK/Ireland, Italian and Spanish cohorts are the largest of the participating cohorts, with 923, 443 and 429 patients aged <18 years in current follow-up respectively.

Of the 1810 patients with HCV serostatus available, 75(4%) were HCV seropositive of whom 34 were in the Russian cohort, 19 in the Thai cohort and 18 in the Spanish cohort. The HCV seroprevalence overall and by cohort may be over-estimated due to targeting testing of patients known to be exposed to HCV.

As shown in the table 9 below, approximately 36% of patients aged <18 years and in current follow-up were taking and NNRTI-based regimen and 45% were taking a boosted PI-based regimen and 11% were not taking any ART.

The proportion of patients not currently on ART in each cohort varied from 2% in the Thai cohort, to 3% in the Spanish cohort, 15% in the UK/Ireland cohort to 25% in the Russian cohort.

**Table 9: ART regimens for patients aged <18 years in current follow-up by cohort, n (row %) (n=2630)**

Cohort	Aged <18 years in current follow-up	ART regimen (n (%))						
		NNRTI + NRTIs	Boosted PI + NRTIs	Unboosted PI + NRTIs	Boosted PI + NNRTI + NRTIs	Unboosted PI + NNRTI + NRTIs	Other ART regimen	Not on ART
Belgium	69	23 (33)	32 (46)	3 (4)	1 (1)	0 (0)	1 (1)	9 (13)
Denmark	27	10 (37)	15 (56)	0 (0)	0 (0)	0 (0)	0 (0)	2 (7)
Italy	443	131 (30)	249 (56)	3 (1)	5 (1)	0 (0)	19 (4)	36 (8)
Portugal	34	7 (21)	20 (59)	0 (0)	3 (9)	0 (0)	2 (6)	2 (6)
Russia	273	35 (13)	149 (55)	14 (5)	2 (1)	0 (0)	4 (1)	69 (25)
Spain	429	135 (31)	213 (50)	12 (3)	21 (5)	0 (0)	33 (8)	15 (3)
Sweden	69	31 (45)	26 (38)	0 (0)	1 (1)	0 (0)	3 (4)	8 (12)
Switzerland	55	17 (31)	29 (53)	0 (0)	1 (2)	0 (0)	6 (11)	2 (4)
Thailand	308	167 (54)	119 (39)	6 (2)	5 (2)	0 (0)	6 (2)	5 (2)
UK/Ireland	923	381 (41)	340 (37)	20 (2)	8 (1)	1 (0)	36 (4)	137 (15)
Total	2630	937 (36)	1192 (45)	58 (2)	47 (2)	1 (0)	110 (4)	285 (11)

**Assessor's comments:**

The context data suggest that ATV is relatively infrequently prescribed to children – with around 14% of HIV-infected children in the contributing cohorts had ever taken any dose of ATV (372 on ATV-containing ART out of 2630 on any ART) and 30% of HIV-infected children receiving boosted PI.

**MAH discussion**

The final report of this 3-year-pharmacovigilance study suggest that ATV was prescribed relatively infrequently in the paediatric HIV-infected population in Europe and in general. ATV-containing regimens, both licensed and unlicensed, appear to be well tolerated in

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the paediatric population of HIV-infected patients, and that discontinuations for adverse events were uncommon. Grade 3 or 4 hyperbilirubinaemia events were reported in 49% of patients with BIL results available (compared with 52% of 2004 adults on ATV in an Italian study) and high incidence rates of grade 3 or 4 BIL events were sustained overtime with a rate of 32 per 100 PY (95% CI 23-44) in the licensed group after >24 months on ATV. Anecdotally, clinicians reported that some children remained clinically well and were not advised to stop ATV. Other laboratory abnormalities and adverse events were reported infrequently. Only 7 non-hyperbilirubinaemia adverse events were considered by the treating physician to be causally related to a licensed dose of ATV: rash; nausea/vomiting and respiratory adverse event; lipodystrophy; proteinuria, symptomatic hepatitis with jaundice; hepatic disease; and diarrhea. Since ATV is taken with ritonavir and other antiviral drugs, it is difficult to attribute causality of these adverse events to any specific agent.

### **3. Rapporteur's Overall Conclusion And further action if required**

Overall Conclusion:

Based on the review of the *final Report "Pharmacovigilance study on the safety and use of atazanavir (ATV) in HIV infected children and adolescents in Europe"* regarding FUM 74 for Reyataz (atazanavir), the Rapporteur concludes the following:

- The context data suggest that ATV is relatively infrequently prescribed to children and the number of paediatric patients is still low to draw firm conclusions regarding the long term safety,
- No new safety issues have been identified at this moment. The safety profile of ATV, based on the review of ADRs reported in paediatric patients receiving ATV-containing cART, is in line with the known safety profile of ATV. The most frequent adverse reactions are hyperbilirubinaemia.

The request from the CHMP has been considered as fulfilled. The MAH will continue to monitor the safety of ATV in paediatric patients through routine Pharmacovigilance activities.