23 April 2009
EMA/632830/2012
Committee for Medicinal Products for Human Use (CHMP)

Kaletra

(lopinavir / ritonavir)

Procedure No. EMEA/H/C/000368/P45/099

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

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

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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Rapporteur's Preliminary Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

P45 - Paediatric Article 45 Follow Up Measure 099

Kaletra (lopinavir / ritonavir)

EMEA/H/C/000368

Marketing Authorisation Holder: Abbott Laboratories Ltd.

Rapporteur:	Pierre Demolis
Start of the procedure:	21 December 2008
Date of this report:	13 March 2009
Deadline for CHMP member's comments:	07 April 2009

INTRODUCTION

As a reminder, Kaletra is indicated for the treatment of HIV-1 infected adults and children above the age of 2 years, in combination with other antiretroviral agents.

Kaletra oral solution 80/20 mg/mL and Kaletra soft gel capsule 133.3/33.3 mg were approved in March 2001. A new formulation, Kaletra 200/50 mg tablet, was approved in June 2006. Finally, a lower dose lopinavir/ritonavir 100/25 mg paediatric tablet formulation received favourable CHMP opinion in January 2008.

The oral solution is the recommended lopinavir/ritonavir formulation for use in small children allowing maximal flexibility and accuracy of dosing. The recommended dose, based on body surface area, is 230/57.5 mg/m2 twice daily taken with food, up to a maximum dose of 400/100 mg twice daily. The recommended dose for the lopinavir/ritonavir 100/25 mg paediatric tablet is 2 to 4 tablets twice daily based on weight (range 15 to 40 kg).

In response to Article 45 of the Paediatric Regulation, a line listing of lopinavir/ritonavir paediatric studies not previously submitted by Abbott was submitted to the EMEA (listed in table 1).

In addition, **a literature search was conducted** to find studies not previously submitted by Abbott. Two studies were found to be relevant in the literature search (listed in table 2). Other studies that did not add significant clinical context and did not adequately support clinical information were excluded (e.g. case reports, studies with a small sample size, and studies with insufficient data).

Moreover, the MAH submitted the reports for two completed paediatric studies for Kaletra (**M99-046 and R&D/04/110**), in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Kaletra and that there is no consequential regulatory action.

SCIENTIFIC DISCUSSION

Non-clinical aspects

The MAH has submitted a report for study TA98-022:
Four-Week Oral Toxicity Study of Abbott-157378 in Combination with Ritonavir (Abbott-84538) in Immature (Juvenile) Rats

Rapporteur's comment:
A 4 weeks study in juvenile rat had been submitted at the time of the initial MA application for KALETRA. It is unclear whether study TA98-022 corresponds to another study and, in the later case to what extent this study provides additional insight as regards the juvenile toxicity.
The MAH should clarify.

Clinical aspects

1. Introduction

In response to Article 45 of the Paediatric Regulation, a line listing of lopinavir/ritonavir paediatric studies not previously submitted by Abbott is listed in table 1.

Table 1. Lopinavir/Ritonavir Studies in Article 45 Line Listing

Study number/ Lead Author/ Title	Study Design	N	Baseline Characteristics	Duration	Results/MAH's Conclusions	Rapporteur's comment
M99-046: (ABT-378/ritonavir) Early Access Program Report provided	Multi-center, multi-country open-label, non-comparative early access study. Not designed to assess efficacy.	14,254	HIV-infected subjects 12 years of age and older who had failed and/or were intolerant to combination therapy with available antiretroviral agents.	No specified duration	**Safety:** 8.9% subjects with SAE. Most common were pneumonia, fever, pancreatitis, and anemia. No safety signals not previously identified were noted in this study.	***Kaletra is already approved for the treatment of children aged 2 years and above at the dose of 230/57.5mg/m2 twice daily. The indication was supported by study M98-940, an open-label study conducted in 100 antiretroviral naïve (44%) and experienced (56%) paediatric patients (aged 6 months to 12 years).*** ***Of note, among the 14 254 subjects enrolled in the EAP, the paediatric population is confined to only 85 patients and these patients are 12-<18 years old.*** ***In agreement with the MAH, EAP cannot be used for assessing efficacy. Preliminary safety data from the first 1290 subjects included in this EAP study was provided at the time of MA. When reviewing the whole safety data from the EAP study, no apparent deviation from the known safety profile of KALETRA is observed. Therefore, no SPC change is requested on the basis of this study.***
NETH 378-00-66: Verweel et al. Plasma	Retrospective non-	23	HIV-1 infected children 0.4-13.2	N/A	**PK:** Mean lopinavir pk parameters similar to	***Insofar that there is an ongoing procedure to explore the possibility***

concentrations of the HIV-protease inhibitor lopinavir are suboptimal in children aged ≤2 years Publication provided *Antiviral Therapy 2007*	comparative study of parmacokinetics of LPV/ritonavir 230/57.5 mg/m^2 twice daily.		y.o who started tt with LPV/r and two NRTIs and underwent a 12-h pharmacokinetic curve at 2-4 wks after start of tt.		previously published data but **exposure significantly reduced in children <2 years old**. **Efficacy:** 93% (14/15) naïve and 66% (2/3) pretreated patients had <50 copies/ml at week 48.	***to extend the indication for KALETRA to children less than 2 years of age in order to answer a medical need, all PK data available on this topic, including data from publication provided in response to article 45, will be discussed in the setting of this FUM (see KALETRA FUM 093).***
NETH 378-00-66: Van der Lee et al. Pharmacokinetics of a once-daily regimen of lopinavir/ritonavir in HIV-1-infected children. Publication provided *Antiviral Therapy 2006*	24 hour pharmacokinetic study of LPV/ritonavir 460/115 mg/m^2 once daily	19	HIV-1 infected children 1.4-12.9 years on stable antiretroviral therapy with a viral load <50 copies/ml for at least 6 months	N/A	**PK:** mean pk parameters comparable to 800/200 mg once daily in adults. Variability in trough levels higher in children than historical adult controls.	***Insofar that the once daily regimen is currently under assessment in adults and has raised major objections, any discussion on once daily regimen in children appears premature at this stage.***

Table 1. continued

Study number/ Lead Author/ Title	Study Design	N	Baseline Characteristics	Duration	Results/Conclusions	Rapporteur's comment
R&D/04/110: **Retrospective Analysis of the Effect of Kaletra (lopinavir/ritonavir) compared with Viracept (nelfinavir) and Norvir (ritonavir) in HIV-Infected Pediatric Patients.** Report provided	Retrospective patient registry/observational Cohort study in Switzerland comparing lopinavir/ritonavir, nelfinavir, and ritonavir.	133	HIV-1 infected children 1.0-17.3 years who had received antiretroviral treatment with at least 1 of the 3 PIs of interest were analyzed. Subjects may have received lopinavir/ritonavir, nelfinavir, and/or ritonavir as a first-, second-, or third line or higher PI-based therapy.	N/A	**Safety:** No clinically relevant differences in AEs between treatment groups. Treatment emergent AEs related to underlying HIV disease. **Efficacy:** Virologic and immunologic response sustained through the first 48 weeks of treatment with lopinavir/ritonavir, nelfinavir, and ritonavir regardless of the line of PI therapy and in second-line PI use.	***44 patients (mean age:10.6 y-o; range:1-20) had received Kaletra in this Phase IV study. This observational cohort study was based on the Switzerland registry database and included subjects who received PI of interest from March 1996 to October 2003.*** ***Given that VIRACEPT and NORVIR (used as an antiretroviral agent) are quite marginalized in the therapeutic management of patients, comparisons made in this study are of poor relevance nowadays.***
HIV-NAT 017: Ananworanich et al. Pharmacokinetics and 24-week efficacy/safety of dual boosted Saquinavir/Lopinavir/ Ritonavir in Nucleoside-pretreated children. Publication provided *The Paediatric Infect Disease Journal 2005*	Open-label, 24 week, single arm pilot study at 2 centers in Thailand to assess pharmacokinetics and 24-week safety and efficacy of saquinavir 50 mg/kg twice daily + lopinavir/ritonavir 230/57.5 mg/m^2 twice daily.	20	HIV-1 infected children age < 16 years, median age 8.5 years. Failing NRTI or NRTI/NNRTI based treatment.	24 weeks	**PK:** Plasma drug concentrations of all three drugs were at the higher limits of expected ranges for adult treatment at approved dosages. **Safety:** Well tolerated. One child with grade 3 diarrhea possibly related. **Efficacy:** 60% with viral load < 50	***Whereas the prominent issue for paediatric patients is to substantiate the use of KALETRA in children below 2 years of age to answer a medical need in this population, no children below 2 years of age were included in this study.*** ***Furthermore, dual boosted PIs become disputable concept, especially given the existing alternatives.***

					copies/ml at 24 weeks.	***No clinically relevant data for paediatric patients are expected to be retrieved from this study.***

Table 1. continued

Study number/ Lead Author/ Title	Study Design	N	Baseline Characteristics	Duration	Results/Conclusions	Rapporteur's comment
ACA-GmbH-01-4: Fraaij et al. Safety and efficacy of a NRTI-sparing HAART regimen of efavirenz and lopinavir/ritonavir in HIV-1-infected children. Publication provided *Antiviral therapy 2004*	Observational, non-comparative pilot study to assess treatment with efavirenz 14 mg/kg once daily and lopinavir/ritonavir 300/75 mg/m^2 twice daily	8	HIV-1 infected children age 5.6-15 years, with genotypic resistance to NRTIs, a CD4 cell count less than the age specific reference value and/or HIV-1 bDNA >1000 copies/ml.	48 weeks	**Safety:** Side effects were transient except for dyslipidemia. No sign of lipodystrophy. Therapy was well tolerated. **Efficacy:** 57.1% (4/7) children with viral load <50 copies/ml. One child lost to follow up.	***Apart from the interest of the concept of the NNRTI sparing regimen which nevertheless remains to be validated in adults, this study cannot be reliably interpreted given the small number of patients included (n=8)***
Rosso et al. Lopinavir/ritonavir exposure in treatment-naive HIV-infected children following twice or once daily administration. Publication provided *Journal of Antimicrobial Chemotherapy 2006*	Pilot pharmacokinetics study to examine exposures to lopinavir/ritonavir 460/115 mg/m^2 once daily for 3 days after lopinavir/ritonavir 230/57.5 mg/m^2 twice daily was administered for at least 1 month. Lopinavir/ritonavir was given in combination with two NRTIs.	28	Treatment naïve HIV-1 infected children age 3.5-15 years with viral load >50 copies/ml.	24 weeks	**PK:** High interindividual variability and low concentrations in some patients were observed. Authors suggest that therapeutic drug monitoring may be useful in children. **Safety:** No significant adverse events were recorded during the 3 days of switch to once daily lopinavir/ritonavir.	***No children below 2 years of age were included in this study.*** ***Insofar that the once daily regimen is currently under assessment in adults and has raised major objections (see ongoing procedure Kaletra I167 to allow OAD administration in naïve adult and adolescent patients)., any discussion on once daily regimen in children appears premature at this stage.*** ***No measures are mandatory on the basis of this study at this stage.***

Table 1. continued

Study number/ Lead Author/ Title	Study Design	N	Baseline Characteristics	Duration	Results/Conclusions	Rapporteur's comment
Larru et al. Long-term response to highly active antiretroviral therapy with lopinavir/ritonavir in pre-treated vertically HIV-infected children. Publication provided *J of Antimicrobial Chemotherapy 2008*	Retrospective study of vertically HIV infected children followed from June 2000 to October 2006 in 8 Spanish paediatric referral hospitals.	69	Vertically HIV-infected children 7.1-11.3 years. Received lopinavir/ritonavir for the first time in a HAART regimen for a duration of at least 12 months after a failure with a previous HAART regimen containing other PIs.	Median duration treatment 57.1 months	**Safety:** Safe and well tolerated. 8.7% with AEs, 4 children with grade 3 diarrhea. Four died of AIDS related illness. 28.6% with any signs of lipodystrophy. **Efficacy:** Ongoing immune recovery with improvements in %CD4+ after 4 years of follow up.	***No children below 2 years of age were included in this study.*** ***Signs of lipodystrophy were noted in 28.6% of children in this 6 years retrospective study, a rate which appears consistent with the prevalence of lipodystrophy reported in HIV-infected children in other studies. Furthermore, as a known risk factor, stavudine was the most prevalent NRTI at baseline in this cohort.***
Kline et al. Long-term follow-up of 414 HIV-infected Romanian children and adolescents receiving lopinavir/ritonavir-containing highly active antiretroviral therapy. Publication provided *Pediatrics 2007*	Observational study of cohort of HIV infected children receiving lopinavir/ritonavir containing HAART between Nov 2001 and Aug 2006 at the Romanian-American Children's Center in Romania.	414	HIV infected children ages 5-18 years, 8% treatment naïve, 82% treatment experienced, 9% with unknown treatment history. Most with moderate or severe HIV associated clinical symptoms and immunosuppression.	Median duration treatment >4 years	**Safety:** 81% remained on therapy after a median duration of >4 years. Thirty-seven deaths were observed, a rate which was noted to compare favorably to prospective historical data. **Efficacy:** 72.5% (192/265) children with HIV RNA <400 copies/ml. Mean change of CD4+ lymphocyte count +270 cells per microliter after 4 years	***No children below 2 years of age were included in this study.*** ***According to the authors, because of the unique epidemiology of pediatric HIV infection in Romania, children and adolescents who were treated with lopinavir/ritonavir-containing HAART were relatively old (mean age: 13 years), and most had acquired the infection horizontally, questioning the extrapolation of the study findings to vertically infected children.*** ***Of note, 37 deaths were observed; most of them occurred among children with advanced HIV disease at the time HAART***

					of treatment.	*was initiated.* ***A specific cause of death was reported in half of the cases.*** *Causes of death included tuberculosis (8 cases), progressive encephalopathy (4 cases), cytomegalovirus disease (3 cases), and pneumonia (2 cases).* ***The mortality rate*** *was 3.3 per 100 patient-years during* ***the first half of the study period (Nov 01 through Dec 03) and was*** *1.2 per 100 patient-years during the second half (Jan 04-Aug 06).* ***Although high, the mortality rate reported in this study seems compatible with the mortality rate of children with evidence of advanced HIV disease progression.*** ***No data are expected to be retrieved from this observational study where children received LPV/rtv in an open label manner in combination with a non-standardized HIV-drugs regimen.***
Resino et al. Antiretroviral activity and safety of lopinavir/ritonavir in protease inhibitor-experienced HIV-infected children with severe-moderate	Prospective multicenter study to study the effectiveness of salvage therapy with lopinavir/ritonavir.	25	HIV infected children ages 3.2-17.1 years, CD4+ <25% and <500 cells/mm^3, virological failure with a PI and/or	18 months	**Safety:** Well-tolerated enabling adherence to treatment. The most common AEs were gastrointestinal and the most common lab abnormality was lipid	***No children below 2 years of age were included in this study.*** ***Efficacy results reported in this study appears consistent with the rate of response***

immunodeficiency. Publication provided *Journal of Antimicrobial Chemotherapy 2006*			NNRTI, viral load >5000 copies/ml.		elevations. **Efficacy:** 47% with viral load <400 at 18 months. Median increase was 15% CD4+ and 300 cells/mm^3.	***expected in heavily pre-treated children when compared to historical data reported with other PIs in ARV-experienced paediatric patients.*** ***Heavily pre-treated children (above the age of 2 years) are already included in the approved therapeutic indications.*** ***No further action is required on the basis of this study.***

Table 1. continued

Study number / Lead Author / Title	Study Design	N	Baseline Characteristics	Duration	Results / Conclusions	Rapporteur's comment
Ramos et al. Safety and antiviral response at 12 months of lopinavir/ritonavir therapy in human immunodeficiency virus-1-infected children experienced with three classes of antiretrovirals. Publication provided *The Pediatric Infectious Disease Journal 2005*	Open label, retrospective, multicenter, observational study of lopinavir/ritonavir therapy in heavily treatment experienced children in 12 Spanish hospitals.	45	HIV-1 infected children age 4.3-17.1 years, HIV RNA >5000, experienced with the NRTIs, NNRTIs, and PIs.	12 months	**Safety:** 40% with AEs. Most common AE was diarrhea (16%). Two patients had grade 3 or 4 hypertriglyceridemia. **Efficacy:** 49% with HIV-1 RNA <400 copies/ml at 48 weeks.	***No children below 2 years of age were included in this study.*** ***Efficacy results reported in this study appears consistent with the rate of response expected in heavily pre-treated children when compared to historical data reported with other PIs in children-experienced patients. Heavily pre-treated children (above the age of 2 years) are already included in the approved therapeutic indications.*** ***No further action is required on the basis of this study.***
DeLuca et al. Different kinetics of immunologic recovery using nelfinavir or lopinavir/ritonavir-based regimens in children with perinatal HIV-1 infection. Abstract provided *Int J Immunopathol*	Observational, retrospective study comparing virologic and immunologic outcomes of regimens containing saquinavir (N=12), nelfinavir (N=18),	40	Children with perinatal HIV-1 infection 1.2-16 years switched from a double therapy with 2 NRTIs or 1NRTI and 1 NNRTI to HAART based	24 weeks	**Safety:** 4 lipodystrophy and 1 diarrhea in nelfinavir group; 1 lipodystrophy and 1 hypertriglyceridemia in lopinavir/ritonavir group. **Efficacy:** Saquinavir-treated children displayed significant reduction in viral load at week 24 (but not at week 4)	***The number of patients aged below 2 years is not specified (but assumed to be very limited)*** ***The limitation of the study design (observational, retrospective study) and the very limited number of***

Pharmacol 2005	or lopinavir/ritonavir (N=10)		upon Italian and USA guidelines.		and no increase in CD4+ T-lymphocyte count. Virologic failure occurred in 33.3% nelfinavir-treated children but in no child receiving lopinavir/ritonavir. Lopinavir/ritonavir-based regimen controlled viral replication more efficiently and restored CD4+ count more quickly than saquinavir- or nelfinavir-based HAART.	***patients included (10-18 per treatment arm) preclude drawing reliable comparison.*** ***Salvage therapy of children is already covered by the therapeutic indications of KALETRA.***
Jullien et al. Population analysis of weight-, age-, and sex-related differences in the pharmacokinetics of lopinavir in children from birth to 18 years. Publication provided *Antimicrobial Agents and Chemotherapy 2006*	Pharmacokinetic study of lopinavir in children using a population model.	157	Children with HIV infection 3 days to 18 years receiving lopinavir as part of their treatment.	N/A	**PK:** Lopinavir volume of distribution and plasma clearance both related to body weight, with an important increase in weight-normalized clearance for the lowest body weight. Combined treatment with lopinavir and nevirapine found to increase clearance. Lopinavir clearance age and sex related; 39% increase observed after the age of 12 years for boys compared to the clearance for girls.	***This study based on a PPK approach identified children younger than 6 months of age and boys older than 12 years of age as subpopulations in which the levels of exposure to lopinavir may be decreased.*** ***Insofar there is an ongoing procedure to explore the possibility to extend the indication for KALETRA to children less than 2 years of age in order to answer a medical need, all PK data available on this topic, including data from publication provided in response to article 45, will be discussed in the setting of this FUM (see KALETRA***

						FUM 093).

Moreover, two studies that were found to be relevant in the literature search are listed in table 2.

Table 2. Additional Relevant Literature for Lopinavir / Ritonavir

Study number / Lead Author / Title	Study Design	N	Baseline Characteristics	Duration	Results / Conclusions	Rapporteur's comment
Resino et al. Positive virological outcome after lopinavir/ritonavir salvage therapy in protease inhibitor-experienced HIV-1-infected children: a prospective cohort study. Publication provided *Journal of Antimicrobial Chemotherapy. 2004, 54; 921-931*	A multicenter, prospective observational study of virological response to lopinavir/ritonavir therapy in PI experienced children.	67	Children with HIV-1 infection 1.4-17.1 years with virological failure to ART with a PI, viral load >5000 copies/ml.	At least 3 months of follow up	**Safety:** 44.7% with AEs. Gastrointestinal most common. Cholesterol and triglyceride increases only abnormal laboratory parameters. **Efficacy:** 65.6% with viral load <400 copies/ml.	***The number of patients aged below 2 years is not specified (but assumed to be very limited)*** ***Safety and efficacy data are consistent with those reported in other studies.*** ***Salvage therapy of children is already covered by the therapeutic indications of KALETRA.*** ***No SPC changes are necessary.***
Resino et al. Salvage Lopinavir-Ritonavir Therapy in Human Immunodeficiency Virus Infected Children. Publication provided *Pediatric Infectious Disease Journal. 2004, 23(10); 923-930*	Retrospective observational study comparing 1) 2 or more NRTIs + 1 PI but not lopinavir/ritonavir who are receiving HAART for the first time 2) PI experienced	120	Children with HIV-1 infection 2.7-16 years with viral load >5000 copies/ml.	>24 months treatment	**Efficacy:** First Line HAART 52.4% with viral load <400 copies/ml. Second Line HAART 48.3% with viral load < 400 copies/ml HAART with lopinavir/ritonavir 71.5% with viral load < 400 copies/ml	***No children below 2 years of age were included in this study.*** ***Efficacy results are consistent with results expected in the targeted population.*** ***Salvage therapy of children***

	children receiving second line HAART but not lopinavir/ritonavir 3) PI experienced children receiving HAART including lopinavir/ritonavir				HAART that includes lopinavir/ritonavir is able to control HIV replication more efficiently than other salvage antiretroviral therapies.	***is already covered by the therapeutic indications of KALETRA.*** ***No SPC changes are necessary.***

Note: ***Given the poor added value of the studies submitted in response to Article 45 of the Paediatric Regulation, more detailed presentation of the studies' design and results would be of limited utility.***

Rapporteur's Overall Conclusion AND RECOMMENDATION

- **Overall conclusion**

Kaletra is currently already approved for the treatment of children aged 2 years and above at the dose of 230/57.5mg/m2 twice daily. The indication was supported by study M98-940, an open-label study conducted in 100 antiretroviral naïve (44%) and experienced (56%) paediatric patients (aged 6 months to 12 years).

Whereas the prominent issue for paediatric patients is to substantiate the use of KALETRA in children below 2 years of age to answer a medical need in this population, a very limited number of children below 2 years of age were included in studies provided in response to article 45 of the Paediatric Regulation.
Furthermore, insofar that there is an ongoing procedure to explore the possibility to extend the indication for KALETRA to children less than 2 years of age, all PK data available on this topic, including data from publications provided in the current procedure, will be discussed in the setting of this FUM (see KALETRA FUM 093).

Overall, no new clinically relevant efficacy data were provided in the studies submitted. Most of the studies pertain to the efficacy of KALETRA in (heavily) treatment-experienced children, a population which is targeted by the approved therapeutic indications of KALETRA.
Most publications are old publications (only 5 published after 2005). Some referred to outdated strategies (dual boosted Protease Inhibitors) or to the use of KALETRA once daily. The use of KALETRA once daily in children appears a premature at this stage insofar that this OAD regimen is currently under assessment in adults and has raised major objections.

Finally, no apparent departure from the known safety profile of KALETRA was observed in the study provided.

Overall, no SPC changes are deemed necessary on the basis of the studies provided in response to article 45 of the Paediatric Regulation.
However, the MAH provided a non-clinical study report relative to juvenile toxicity (study TA98-022) without discussing the impact of this study as regards the already available data on this topic. Therefore, the MAH should clarify to what extent study TA98-022 provides additional insight as regards the juvenile toxicity of KALETRA.

- **Recommendation**

☐ **Fulfilled –**

☒ **Not fulfilled:**
The MAH should clarify to what extent study TA98-022 provides additional insight as regards the juvenile toxicity of KALETRA.

ADDITIONAL CLARIFICATIONS REQUESTED

The MAH should clarify to what extent study TA98-022 provides additional insight as regards the juvenile toxicity.

A 30 day response timetable without clock stop will apply.

In response to Article 45 of the Paediatric Regulation, a line listing of lopinavir/ritonavir paediatric studies not previously submitted by Abbott was submitted to the EMEA (listed in table 1).

In addition, **a literature search was conducted** to find studies not previously submitted by Abbott. Two studies were found to be relevant in the literature search (listed in table 2). Other studies that did not add significant clinical context and did not adequately support clinical information were excluded (e.g. case reports, studies with a small sample size, and studies with insufficient data).

Moreover, the MAH submitted the reports for two completed paediatric studies for Kaletra (**M99-046 and R&D/04/110**), in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Kaletra and that there is no consequential regulatory action.

The conclusions of the last report were as follows:

Overall, no new clinically relevant efficacy data were provided in the studies submitted. Most of the studies pertain to the efficacy of KALETRA in (heavily) treatment-experienced children, a population which is targeted by the approved therapeutic indications of KALETRA.

Most publications are old publications (only 5 published after 2005). Some referred to outdated strategies (dual boosted Protease Inhibitors) or to the use of KALETRA once daily. The use of KALETRA once daily in children appears a premature at this stage insofar that this OAD regimen is currently under assessment in adults and has raised major objections.

Finally, no apparent departure from the known safety profile of KALETRA was observed in the study provided.

Overall, no SPC changes are deemed necessary on the basis of the studies provided in response to article 45 of the Paediatric Regulation.

However, the MAH provided a non-clinical study report relative to juvenile toxicity (study TA98-022) without discussing the impact of this study as regards the already available data on this topic. **Therefore, the MAH should clarify to what extent study TA98-022 provides additional insight as regards the juvenile toxicity of KALETRA.**

Assessment of Applicant's responses to RSI

The applicant's response to the RSI was as follows:

"Study TA98-022 was included as it was data that had not been submitted to the EMEA and as it was juvenile toxicity study, the study could be considered relative to the article 45 initiative. However, TA98-022 provides no new data that would indicate a change in the risk/benefit profile of lopinavir/ritonavir or warrant a change in the labelling."

Rapporteur's comment:
The submission of study TA98-022 as a stand-alone non-clinical report is not acceptable. The applicant is requested to provide an expert's critical discussion regarding this report to justify the assumption that no new data emerged from this study that would change the risk/benefit of Kaletra or warrant a change in product information.

In response to Article 45 of the Paediatric Regulation, a line listing of lopinavir/ritonavir paediatric studies not previously submitted by Abbott was submitted to the EMEA (listed in table 1).

In addition, **a literature search was conducted** to find studies not previously submitted by Abbott. Two studies were found to be relevant in the literature search (listed in table 2). Other studies that did not add significant clinical context and did not adequately support clinical information were excluded (e.g. case reports, studies with a small sample size, and studies with insufficient data).

Moreover, the MAH submitted the reports for two completed paediatric studies for Kaletra (**M99-046 and R&D/04/110**), in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Kaletra and that there is no consequential regulatory action.

The conclusions of CHMP following first tour assessment (outcome fax on 24 April 2009) were as follows:

"Overall, no new clinically relevant efficacy data were provided in the studies submitted. Most of the studies pertain to the efficacy of KALETRA in (heavily) treatment-experienced children, a population which is targeted by the approved therapeutic indications of KALETRA.
Most publications are old publications (only 5 published after 2005). Some referred to outdated strategies (dual boosted Protease Inhibitors) or to the use of KALETRA once daily. The use of KALETRA once daily in children appears a premature at this stage insofar that this OAD regimen is currently under assessment in adults and has raised major objections.

Finally, no apparent departure from the known safety profile of KALETRA was observed in the study provided.

Overall, no SPC changes are deemed necessary on the basis of the studies provided in response to article 45 of the Paediatric Regulation. "
However, the MAH provided a non-clinical study report relative to juvenile toxicity (study TA98-022) without discussing the impact of this study as regards the already available data on this topic. ***Therefore, the MAH should clarify to what extent study TA98-022 provides additional insight as regards the juvenile toxicity of KALETRA."***

In response to the RSI 1 the applicant stated that:
"Study TA98-022 was included as it was data that had not been submitted to the EMEA and as it was juvenile toxicity study, the study could be considered relative to the article 45 initiative. However, TA98-022 provides no new data that would indicate a change in the risk/benefit profile of lopinavir/ritonavir or warrant a change in the labelling."

However, the CHMP considered that the submission of study TA98-022 as a stand-alone non-clinical report was not acceptable. The applicant was requested (RSI2) to provide an expert's critical discussion regarding this report to justify the assumption that no new data emerged from this study that would change the risk/benefit of Kaletra or warrant a change in product information.

Assessment of Applicant's responses to RSI 2

The applicant's response to the RSI2 was as follows:

In the 4-week juvenile toxicity study in rats that was dosed at 0/0, 10/5, 30/15 or 100/50 mg/kg lopinavir/ritonavir, there were no treatment-related deaths, changes in behaviour or physical condition of the animals. Body weight and food consumption were decreased at the highest dosage. Microscopic changes included centrilobular hepatocytomegaly and thyroid follicular cell hypertrophy and/or hyperplasia at the mid and high-dosages. The hepatocytomegally was associated with increases in serum ALT and liver weights and was suggestive of an induction response for hepatic glucuronosyl transferase. The thyroid changes may have been secondary to hepatic enzyme induction. **Since the mild liver and thyroid changes at 30/15 mg/kg/day were not accompanied by relevant alternations in clinical chemistry parameters or decrements in body weight and food consumption, this dosage was considered to the be No-observed adverse- effect level (NOAEL).**

The target organ changes observed in the liver and thyroid of this study **are generally similar to those previously observed in adult rats** administered the drug combination at the same dosages. Plasma exposures to lopinavir and ritonavir were similar or greater in juvenile animals compared to what has been achieved in adults indicating that juvenile animals do not have an increased sensitivity to the adverse effects associated with the combination of lopinavir/ritonavir. **Overall, the findings in juvenile rats treated with lopinavir/ritonavir are not unexpected and do not represent either a new finding or a more severe manifestation of what has been well characterized in adult rats**.

Rapporteur's comment:
As requested, the Applicant has submitted a brief summary of results for study TA98-022 and concludes that "the findings in juvenile rats treated with lopinavir/ritonavir are not unexpected and do not represent either a new finding or a more severe manifestation of what has been well characterized in adult rats".

However, the Applicant did not clarify in his response to what extent this study differs to the one previously submitted in support to the paediatric indication.

There are similarities between characteristics of study mentioned in EPAR, CHMP initial assessment report for MA and TA98-022 study: age of the juvenile rat, duration of administration of lopinavir/ritonavir, maximum administered dose. Indeed TA98-022 could have been submitted for MMA process for the report of this study was finalised in 1998.

However, there is a discrepancy concerning NOAEL which is estimated to be 10/5 mg/kg/day in CHMP documents and which is estimated to be 30/15 mg/kg/day in TA98-022 report.

Following an e-mail request of the Afssaps/PTL to clarify to what extent this study differs to the one previously submitted in support to the paediatric indication, the Applicant confirmed, by mail dated 8th October 2010, that "the study submitted with the MA application and the Study TA98 022 submitted in response to Article 45 was indeed the same" and that it was mistakenly re-submitted through the Article 45 procedure.

Taking into account
- the previous opinion of CHMP that "no SPC changes are deemed necessary on the basis of the studies provided in response to article 45 of the Paediatric Regulation"
- the data provided by the Applicant and especially the Applicant's mail dated 08/10/10,
it could be considered that follow-up measure (FUM) KALETRA P45 099.2 is fulfilled.

However, as part of a separate new FUM, the Applicant should confirm officially that study TA98 022 submitted in response to Article 45 was indeed the same that study submitted in the Marketing Authorisation Application and that it was mistakenly re-submitted through the Article 45 procedure. Moreover, the Applicant should explain the discrepancy

concerning NOAEL which is estimated to be 10/5 mg/kg/day in CHMP documents and which is estimated to be 30/15 mg/kg/day in TA98-022 report.

Rapporteur's Overall Conclusion And further action if required

KALETRA P45 099.2

Overall Conclusion:

It could be considered that follow-up measure (FUM) KALETRA P45 099.2 is fulfilled.

However, as part of a separate new FUM to be answered within one month, the Applicant should officially confirm that study TA98 022 submitted in response to Article 45 was indeed the same as the study submitted in the Marketing Application and that it was mistakenly re-submitted through the Article 45 procedure. Moreover, the Applicant should explain the discrepancy concerning NOAEL which is estimated to be 10/5 mg/kg/day in CHMP documents and which is estimated to be 30/15 mg/kg/day in TA98-022 report.

☒ PAC fulfilled (all commitments fulfilled) - No further action required

☐ PAC not fulfilled (not all commitments fulfilled) and further action required:

Addendum to Assessment report P45 099

On 23 July 2009 the MAH received positive opinion for a once daily dosing regimen of Kaletra tablets for antiretroviral treatment in naïve adult patients and on 18 February 2010 for a once daily dosing regimen of Kaletra tablets for experienced antiretroviral treatment adult patients.

In addition, subsequent to the date of the assessment report, the MAH fulfilled the requests identified on page 17 of the report (i.e., the request that the MAH confirm that study TA98 022 was the same study submitted in the original Marketing Application and addressed the apparent discrepancy concerning NOAL values).