17 December 2015
EMA/2830/2016
Procedure Management and Committees Support Division

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

Prezista

darunavir

Procedure no: EMEA/H/C/000707/P46/071

Note

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

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Table of contents

1. Introduction

On 10 September 2015, the MAH submitted a completed paediatric study for PREZISTA, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure(s).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study No. TMC114-EPPICC ("The final annual report of a 5-year study of the long-term safety profile of darunavir/ritonavir in HIV-1-infected children and adolescents in the European Union.") is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

In this study an oral suspension of DRV was used. A line extension was granted for ART-experienced paediatric patients (3 to 17 years of age and weighing at least 15 kg) in 2012.

2.3. Clinical aspects

2.3.1. Introduction

Prezista contains the active substance darunavir (DRV, also known as TMC114), which is a potent human immunodeficiency virus (HIV-1) protease inhibitor (PI). It was approved by the EMA in July 2009, in combination with other antiretroviral medicinal products and low dose ritonavir (rtv), for the treatment of HIV infection in antiretroviral therapy (ART) experienced paediatric patients from 6 to < 18 years, based on the results of trial TMC114-C212 (including 80 subjects). At the same time, two other trials were initiated in 2009 in HIV-infected paediatric patients. Study TMC114-TiDP29-C228 (ARIEL) in treatment-experienced children aged from 3 to < 6 years and weighing between 10 kg and < 20 kg was finalised in 2012. In this trial an oral suspension of DRV was used. A line extension was granted for ART-experienced paediatric patients (3 to 17 years of age and weighing at least 15 kg).

The current indication of Prezista is:

PREZISTA, co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult and paediatric patients from the age of 3 years and at least 15 kg body weight.

The RMP identified a lack of information on long-term safety in paediatric patients aged 6 to 18 years of age and the MAH committed in April 2009 to carry out post-marketing research to further characterise the safety profile of DRV/rtv use in paediatric patients in Europe, in the context of the filing of the indication in treatment experienced paediatric patients.

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 DRV in children and adolescents in the European Union.

This report covers the following post-authorisation commitments undertaken by the MAH:

FUM 051 Pharmacovigilance study to define the long-term safety profile of darunavir/ritonavir in HIV-1-infected children and adolescents in Europe

This 5-year pharmacovigilance study is a category 3 additional PhV study per RMP of Prezista to address long term safety profile of darunavir/ritonavir in HIV-1 infected children (3-11 years old) and adolescents (12-<18 years old) weighing at least 15 kilograms. This study was requested in 2009 in the context of granting the indication in treatment experienced paediatric patients. The MAH has already submitted four annual reports during this 5-year period; no new safety information has been identified in the pervious four annual reports of this study.

In the last year of the study covered by this report, three new cohorts have joined the study: a cohort from the Netherlands, from Latvia and from Portugal. In the current submission, the final, fifth report (dated September 2015) is assessed.

2.3.2. Clinical study

This report describes findings of the fifth and final year of this study (children reported to EPPICC cohorts as of 12 March 2015) and includes children in the previous reports with extended follow-up time, including those discontinuing DRV within the reporting period, as well as additional children starting a DRV-based regimen since the last data merger.

This report includes patients from three new cohorts who have joined the EPPICC network this year; the ATHENA cohort in the Netherlands and a cohort from Latvia and the Lisbon cohort from Portugal, increasing the coverage of paediatric HIV patients in Europe. Lastly, as of November 2014, DRV q.d dose was approved for children aged 3-<11 years, one child included in this data merger who initiated DRV on this dose after this date. In the last (fifth) year of the study covered in the current report, there were 531 patients ever on darunavir in the participating cohorts.

The primary objective of this pharmacovigilance study (FUM 051) was:

The overall aim of this ongoing study was to collect long-term safety data on DRV/rtv use in paediatric patients with HIV infection in a "real world" setting in the following 16 countries: Belgium, Denmark, Germany, Italy, Latvia, Netherlands, Poland, Portugal, Romania, Russia, Spain, Sweden, Switzerland, Thailand and the UK/Ireland. Countries newly contributing data this year were Latvia and the Netherlands.

The secondary objectives were:

- To describe the clinical characteristics of HIV-infected paediatric patients aged 3 to <18 years and treated with DRV/rtv in Europe
- To describe off-label use of DRV/rtv in paediatric patients <3 years of age (excluding in utero exposure)

Overall 17 cohorts contributed to this EPPICC report, 16 are mother-child and/ or paediatric cohorts and one single centre cohort of paediatric patients in Romania with parenteral (nonrecreational injecting drug use) HIV transmission, all cohorts provided individual patient data for this study. HIV-infected paediatric patients aged <18 years who were on or had ever received DRV were included. Data were analysed separately for six groups of patients based on the dose given when they first started DRV. Division of AIDS (DAIDS) gradings for paediatric adverse events were used to categorise the severity of laboratory results (absolute neutrophil counts, total cholesterol, triglycerides, alanine transaminase, total bilirubin, fasting plasma glucose, non-fasting plasma glucose, pancreatic amylase, and lipase) and clinical events.

Data collected included demographics, deaths and losses to follow-up, as well as follow-up data (both pre- and post-DRV) for patient weights, ART, AIDS events, CD4 and HIV-1 RNA, key haematology and biochemistry results, and adverse events. The inclusion criteria for the study were as follows: HIV-infected paediatric patients aged <18 years; and who are currently receiving or have ever received DRV. Periods of time in MAH trials were excluded from the analysis in order to avoid duplicate analyses.

Information on demographic characteristics, ART treatment, and adverse events occurring while on DRV were summarised separately for patients who initiated DRV in accordance to therecommended dose for weight, age and RTV co-administration (on-label) and those who did not (off-label), as listed below:

- 3-<18 years taking a licensed dose of DRV/r b.i.d. (or within a window of ±20% of the licensed dose)
- 12-<18 years, weight ≥40kg, taking the licensed dose of 800mg DRV/r q.d.
- 3-<12 years, weight ≥15kg taking a licensed dose of DRV/r q.d
- 3-<18 years taking an unlicensed dose or unboosted DRV
- 0-<3 years
- 3-<18 years, with missing weight or dose

The number of patients and laboratory tests and severity of events are reported in four distinct time periods: (i) 12-months pre-DRV; (ii) < 12-months since start of DRV; (iii) 12-24 months of DRV; and (iv) >24 months of DRV. In this year's report only children with ≥3 months follow up after start of DRV were included in the analysis of laboratory tests. A child can contribute to multiple time periods based on the duration of follow up and availability of laboratory data, although he/she can only be counted once within each grade category (with grades 3 and 4 counted together) within each time period.

Rates of first events are reported in each time period after start of DRV per 100 patient years for patients aged 3 to <18 years (groups i, ii, and iv) with ≥3 months on DRV to allow for the opportunity of laboratory monitoring (group iii was not included as the single patient had <3 months of follow up after start of DRV and no laboratory data). Rates were reported where there were ≥20 patients in follow up within each group-treatment period. Rates are not calculated for children aged<3 years and small groups in other dosing categories due to small sample sizes, or for the 12-month period pre-DRV due to the complex ART treatment histories of many patients starting DRV. All lab tests conducted >30 days after DRV discontinuation are excluded from all analyses with the aim of better assessing events while on DRV.

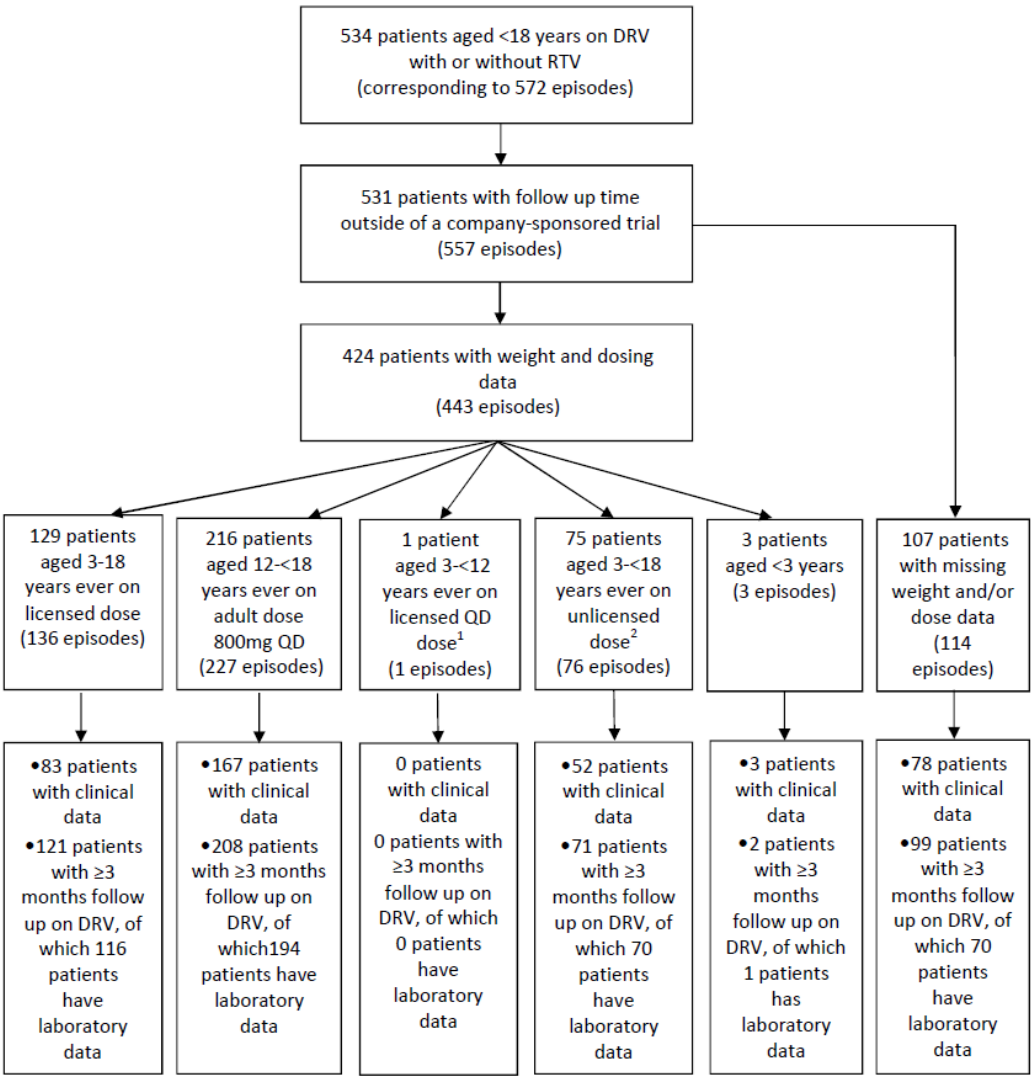
Clinical adverse events are reported for all patients (irrespective of duration on DRV), if the event occurred within 1 month after discontinuation of DRV.

Data review

Results

Data are presented for all paediatric patients who took DRV and were reported to an EPPICC cohort by 12th March 2015. Cumulatively 17 cohorts from 16 countries provided data, including the Lisbon cohort, the Latvian cohort and the ATHENA cohort from the Netherlands which joined in this study for the first time this year. Overall, 534 patients had ever taken any dose of DRV as of 12th March 2015. Three patients out of 534 were excluded from the study as they had follow up only within MAH-sponsored studies. See figure 1 below.

Figure 1 Flowchart of patients and first episodes on DRV



Characteristics of patient taking DRV

Out of 531 patients, 44% were black African, and almost all (95%) were infected with HIV through mother to child transmission. A total of 36% had been diagnosed with AIDS and 6 patients died during the follow up time.

The median age at the start of any ART regimen was 2.0 years for the licensed b.i.d. dose group, and the median age at the start of a DRV-containing regimen was 14.5 years overall, very similar to the ages reported in last year's report, despite an 23% increase in number of patients reported (from 431 patients in 2014 to 531 patients in 2015). Around 16% of patients across all groups had discontinued DRV at last follow-up, a slight increase from the 11% reported last year. The median time on a DRV regimen was 28 months for those in the licensed b.i.d. dose group, and 19 months overall, comparable to the durations reported last year.

Table 1 Antiretroviral therapy profile of all paediatric patients taking DRV (n=531)

ART profile	Treatment status (n (%))						
	Aged 3-<18 years on licensed b.i.d dose (n=129)	Aged 12-<18 years on licensed 800mg q.d dose (n=216)	Aged 3-<12 years on licensed q.d dose (n=1)	Aged 3-<18 years only ever on unlicensed dose (n=75)	Age 0-<3 years (n=3)	Missing weight or dose (n=107)	Total (n=531)
Age starting ART (yrs of age)							
Median age at ART start	2 [0.6,4.8]	6.3 [2.4,11.1]	5.3	2.9 [0.5,6]	0.2 [0,0.3]	2.4 [0.6,5.6]	3.5 [1,8.2]
Age starting DRV (yrs of age)							
<6 years	3 (2)	0 (0)	0	4 (5)	3 (100)	1 (1)	11 (2)
6-8 years	9 (7)	0 (0)	1	7 (9)	0 (0)	8 (7)	25 (5)
9-11 years	20 (16)	8 (4)	0	32 (43)	0 (0)	13 (12)	73 (14)
12-14 years	42 (33)	94 (44)	0	24 (32)	0 (0)	38 (36)	198 (37)
15-<18 years	55 (43)	114 (53)	0	8 (11)	0 (0)	47 (44)	224 (42)
Median age at DRV start	14.1 [12,15.9]	15.1 [13.7,16.3]	6.3	11.2 [10,13.7]	2.2 [2,2.2]	14.6 [12.3,16.5]	14.5 [12.4,16]
Duration on ART before DRV (yrs)							
<2 years	3 (2)	34 (16)	1	12 (16)	2 (67)	9 (8)	61 (11)
2-4 years	7 (5)	37 (17)	0	10 (13)	1 (33)	4 (4)	59 (11)
5-9 years	40 (31)	54 (25)	0	22 (29)	0 (0)	26 (24)	142 (27)
≥10 years	79 (61)	89 (41)	0	30 (40)	0 (0)	67 (63)	265 (50)
Unknown	0 (0)	2 (1)	0	1 (1)	0 (0)	1 (1)	4 (1)
Median duration	11.3 [7.1,12.8]	8.4 [3.7,13.1]	1.0	8.5 [4.4,11.1]	1.9 [1.8,2.2]	11 [7.9,13.8]	10 [5.3,12.9]
ART history before DRV							
Naive	2 (2)	22 (10)	0	9 (12)	0 (0)	6 (6)	39 (7)
1-7 ART drugs	55 (43)	135 (63)	1	48 (64)	2 (67)	50 (47)	291 (55)
8+ ART drugs	72 (56)	59 (27)	0	18 (24)	1 (33)	51 (48)	201 (38)
VL at DRV start							
Value present	76 (59)	164 (76)	0	56 (75)	2 (67)	58 (54)	356 (67)
<=400	34 (45)	97 (59)	-	34 (61)	0 (0)	24 (41)	189 (53)
>400	42 (55)	67 (41)	-	22 (39)	2 (100)	34 (59)	167 (47)
Median VL (log10c/ml)	3 [1.9,4.1]	2.3 [1.6,3.3]	-	2.2 [1.6,3.7]	4.2 [3.7,4.7]	2.8 [2,4.2]	2.5 [1.7,3.7]
CD4 at DRV start							
Value present	99 (77)	180 (83)	0	66 (88)	2 (67)	64 (60)	411 (77)
Missing	30 (23)	36 (17)	1	9 (12)	1 (33)	43 (40)	120 (23)
Median CD4 count (c/mm3)	437 [260,670]	523.5 [320,782]	-	674 [353,953]	1875.5 [1516,2235]	422 [223,698]	519 [300,784]
CD4% at DRV start							
Value present	94 (73)	177 (82)	0	64 (85)	2 (67)	64 (60)	401 (76)
Missing	35 (27)	39 (18)	1	11 (15)	1 (33)	43 (40)	130 (24)
Median CD4%	19.8 [12.9,28]	26 [17,34]	-	27 [19.7,34.5]	32.5 [26,39]	22.4 [13.5,30.5]	24 [16,32]
Time on DRV							
Total patient years on DRV	339	318	-	119	9	216	1000
DRV duration:							
<12mths	26 (20)	87 (40)	0	28 (37)	1 (33)	32 (30)	174 (33)
12-24mths	26 (20)	59 (27)	0	24 (32)	0 (0)	24 (22)	133 (25)
>24 mths	75 (58)	63 (29)	0	21 (28)	2 (67)	45 (42)	206 (39)
Unknown	2 (2)	7 (3)	1	2 (3)	0 (0)	6 (6)	18 (3)
Median time on DRV (months)	28.1 [14.5,45.1]	15.2 [6.6,26.3]	-	15.6 [9.4,29.3]	47.6 [0.9,56.4]	19.4 [9.7,37.7]	18.8 [8.7,33.7]

CHMP's comments:

The number of children and adolescents participating in the study has increased from 123 patients in the first year (2011) of the study to 531 in the final year.

Despite of this increase, the children who received darunavir for the first time when they were under the age of 12 are less represented in the study population. The largest proportion of children received darunavir for the first time when they were 12-<18 year old (422, 79%), while a smaller proportion of children received darunavir for the first time when they were < 12 years old (109/531, 21%) with the smallest proportion of children under age of 6 (11, 2%).

The small number of children below 12 years old, and especially below 6 years could be explained by the fact that darunavir was indicated in older children for a longer period of time and the indication in children < 6 years old was granted only in 2014.

Laboratory data

In general the numbers and rates of grade ≥3 adverse laboratory events were low.

Licensed b.i.d. dose of DRV
Laboratory toxicity data were available for 116 patients aged 3-<18 years on the licensed b.i.d. dose of DRV.

There were 1086 absolute neutrophil count (ANC) test results for 107 patients. Three patients had one or more ANC grade 3 or 4 event (5 events), all occurred during the first 12 months of DRV. The incidence rate of a grade ≥3 ANC test in the first 12- months after start of DRV was 3 per 100 PY (95% CI 1-10), which is similar to the rate reported last year.

There were 917 total cholesterol (CHOL) results for 110 patients. Fifty-five patients had at least one grade 2 event on DRV, giving an overall incidence rate for this grade of 23 per 100 PY (95% CI 17-30). The incidence of grade 2 hypercholesterolemia was 73 per 100 PY (95% CI 53-98) in the first 12 months on DRV, and declined to 51 per 100 PY (95% CI 35-72) at 12-24 months and declined further to 22 per 100PY (95%CI, 14-32) >24 months after start of DRV. These rates are comparable to those reported last year. The number of grade 3 or 4 CHOL results on DRV remained reassuringly low, with 11 events reported among seven patients; eight events occurred <12 months on DRV, one at 12-24 months, and two after >24 months.

916 triglyceride (TRIG) test results were reported for 112 patients. Four patients had at least one grade 3 or 4 test result (8 events) whilst taking DRV; four grade ≥3 results were reported during the first 12 months on DRV, three at 12-24 months and one after >24 months.

There were 1,132 alanine transaminase (ALT) test results for 113 individual patients, none had grade ≥3 results on DRV.

Of 97 patients tested for total bilirubin (BIL) levels, three had at least one grade ≥3 result (17 events) on DRV: eight grade ≥3 results were reported during the first 12 months, five at 12- 24 months and four after >24 months on DRV. In last year's report there were five patients with at least one grade ≥3 BIL result on DRV, however events among two patients have been excluded as one patient had <3 months on DRV, while the other was based on incorrect laboratory upper limits which has now been corrected and confirmed they were not grade ≥3 events.

There were no grade ≥3 results for fasting plasma glucose (FPG), among 74 patients tested.

One of the 27 patients tested for non-fasting plasma glucose (non-FPG), had a grade ≥3 result after >24 months on DRV.

Three of 57 children tested for pancreatic amylase (P-AMY) levels had at least one grade 3 or 4 result (5 events), two occurring during the first 12 months on DRV, two at 12-24 months and one after >24 months on DRV. There were no grade ≥3 events reported for lipase (LIP) out of 23 children with test results available.

Licensed 800mg q.d. dose
Laboratory results were available for 194 patients aged 12-<18 years on the licensed 800mg q.d. dose of DRV with laboratory data available, and with >3 months of follow-up. One or more grade ≥3 result was reported for each of the following: CHOL (two events among 998 tests in 184 children), ALT (one event among 987 tests in 160 children), BIL (four events among 1117 tests in 167 children), FPG (one event among 170 tests in 37 children), non-FPG (one event among 340 tests in 75 children) and P-

AMY (one event in 315 tests in 55 children), all except the ALT and FPG events occurred within 12 months of starting DRV. There were no grade ≥3 results on the 800mg q.d. dose of DRV for triglycerides or lipase.

Unlicensed dose

Nine patients aged 3-<18 years on an unlicensed dose of DRV experienced grade 3 and 4 events. Five were previously reported last year. Seven patients had grade ≥3 ANC results, and six remained on DRV, three of whom subsequently had a "normal" result; the other patient remained on DRV for more than two years after the event before discontinuing due to treatment failure. Two patients had a grade 3 BIL event, one had a subsequent "normal" result, while the other did not, both remained on DRV. One patient had a grade 3 CHOL event (as well as a grade 3 ANC result), remained on DRV despite not having a "normal" subsequent test result.

There were no grade ≥3 observations in children aged 0-<3.

CHMP's comments:

The rates of grade ≥3 laboratory events in the fifth year of the study remained low and were comparable to those observed in the last year study period. The review of the adverse laboratory events did not indicate new safety issues in the study population. The adverse events (including adverse laboratory events) considered by the treating physician to be related to darunavir are discussed below in the section on adverse events related to darunavir.

Adverse events related to darunavir

Adverse events reported as related to DRV b.i.d. dose

Clinical data were available for 83 patients on the *licensed b.i.d. dose*. DRV related adverse events were reported in **four** subjects (five events); all were described in last year's report: two adverse events of hypercholesterolemia, both serious, two non-serious adverse event of raised triglycerides and one of rash categorised as serious which led to treatment discontinuation. All events were resolved except for the hypercholesterolemia, for which there is no further information available. See also table 2 below.

Table 2 Clinical adverse events for patients aged 3-<18 years on licensed b.i.d. dose which were considered to be causally related to DRV (n=83 with clinical data)

Patient	Cohort	DRV start date	DRV end date (reason for stopping)	Adverse event	Date event diagnosed	Adverse event resolved (Date if known)	Causally linked to DRV	Whether adverse event considered serious	If serious, whether life threatening	Other ART drugs at time of diagnosis	Age at clinical event (years)	Concomitant medication
1	Sweden	04/06/2007	01/09/2010 (Dyslipidaemia)	Raised triglycerides	17/03/2009	Yes	Definitive	No	No	3TC+EFV+RTVI	16.6	No
				Raised cholesterol	17/03/2009	Yes	Definitive	Yes	No	3TC+EFV+RTVI	16.6	No
2	Spain	14/07/2008	21/12/2010 (Other causes)	Raised triglycerides	25/06/2009	Yes	Definitive	No	No	ETV+RAL+RTVI	16.4	No
3^	Spain	15/04/2010	26/04/2010 (Hypersensitivity reaction)	Severe cutaneous rash	26/04/2010	26/05/2010	Probable	Yes	No	ETV+MRV+RTVI	9.9	No
4	Spain	07/12/2010	24/02/2011 (Dyslipidaemia)	Raised cholesterol	12/02/2011		Definitive	Yes	Yes	RTVI	15.5	No

Adverse events reported as related to DRV 800mg q.d dose

Three patients experienced adverse events, all non-serious, were reported as definitively, probably or possibly causally related to DRV in the patients on the licensed 800mg q.d dose (n=167 with clinical data); all were reported last year, one patient had raised triglycerides, another had rash and the third

had other skin changes. Two patients remained on DRV, one patient discontinued the drug 8 months after the event with reason given as patient's wish/decision. See also table 3.

Table 3 Clinical adverse events for patients aged 12-<18 years on licensed 800mg q.d. dose which were considered to be causally related to DRV (n=167 with clinical data)

Patient	Cohort	DRV start date	DRV end date (reason for stopping)	Adverse event	Date event diagnosed	Adverse event resolved (Date if known)	Causally linked to DRV	Whether adverse event considered serious	If serious, whether life threatening	Other ART drugs at time of diagnosis	Age at clinical event (years)	Concomitant medication
1	Sweden	25/05/2011	Still on drug	Raised triglycerides	07/12/2011	.	Definitive	No	.	3TC+ABC+RTVl	18.2	No
2	Italy	12/03/2012	Still on drug	Rash, erythema	23/03/2012	Yes	Possible	No	.	3TC+EFV+ETV+RTVl+ZDV	12.9	No
3	Italy	14/04/2011	01/04/2013 (Patient's wish/decision)	Other skin changes	09/08/2012	.	Probable	No	.	FTC+RTVl+TDF	17.1	No

Adverse events reported as related to DRV unlicensed dose

Three patients experienced a combined total of six adverse events considered possibly causally related to DRV in patients taking an unlicensed dose (n=52, with clinical data), all were newly reported this year. One patient had a rash and two patients reported abdominal pain, epigastric pain and diarrhoea related events (one patient had a subsequent event of raised triglycerides). All events except the event of raised triglycerides were resolved and all patients remained on DRV. See also table 4.

Table 4 Clinical adverse events for patients aged 3-<18 years on unlicensed dose which were considered to be causally related to DRV (n=52 with clinical data)

Patient	Cohort	DRV start date	DRV end date (reason for stopping)	Adverse event	Date event diagnosed	Adverse event resolved (Date if known)	Causally linked to DRV	Whether adverse event considered serious	If serious, whether life threatening	Other ART drugs at time of diagnosis	Age at clinical event (years)	Concomitant medication
1*	UK/Ireland	26/07/2011	Still on drug	post switch rash, itchy, not seen by staff - self resolved	26/07/2011	Yes	Possible	No	.	3TC+MRV+RTVl	12.9	No
2*	Spain	10/02/2012	Still on drug	Abdominal pain, epigastric pain	30/03/2012	Yes	Possible	No	.	ABC+ddI+RTVl	8.3	No
				Diarrhoea, loose stool, unspecified or <30 days	30/03/2012	Yes	Possible	No		ABC+ddI+RTVl	8.3	No
3*	Spain	15/03/2012	Still on drug	Abdominal pain, epigastric pain	08/06/2012	Yes	Possible	No	.	ABC+ddI+RTVl	8.5	No
				Diarrhoea, loose stool, unspecified or <30 days	08/06/2012	Yes	Possible	No	.	ABC+ddI+RTVl	8.5	No
				Raised triglycerides	10/09/2014		Possible	No	.	ABC+ddI+RTVl	10.8	No

Adverse events reported in the age group 0-<3 years

There were no events considered to be causally related to DRV among the three patients aged 0-<3 years with clinical data.

Adverse events reported in patients with missing weight or dose data

Among the 78 patients with missing weight/dose data, **one patient** experienced clinical events considered causally related to DRV (raised triglycerides and cholesterol, not considered serious).

SAEs reported by the clinician as unlikely to be or not causally related to DRV

Eight patients on the licensed b.i.d. dose had serious adverse events, of which five were reported last year: one case of infectious gastroenteritis, one case of measles, one case of acute otitis media and two deaths. The deaths were due to a HIV-related metastatic adenocarcinoma, and an AIDS-defining event. Additionally a new case of rash was reported this year, a new case of anaemia and a case of decreased visual acuity, all were categorised as serious, and the cases of rash and anaemia were reported as being resolved while the latter was not.

Of 167 patients on the licensed 800mg q.d. dose with clinical data, there were two SAEs unrelated to DRV or where causal link with DRV was not reported or unknown; one patient died due to a non-AIDS defining cancer which was reported last year and one new case of indigestion, oesophageal reflux,

gastritis was reported though this event resolved and the patient remained on DRV. Among the 52 patients on unlicensed dose with clinical data, there was one death from an AIDS defining event (cytomegalovirus colitis with systemic involvement) leading to shock/heart failure, previously reported last year (although the patient was wrongly categorised in the licensed group last year). No SAEs which were not considered to be causally related to DRV were reported for patients 0-<3 years. Clinical data was not available in the one patient aged 3-<12 years on a DRV q.d dose.

Among patients with missing weight or dose, there were two deaths, both reported in last year (one patient has moved across dosage groups this year): one due to post liver transplant complications, the second was due to an invasive bacterial infection. The causal relationship with DRV was unknown in both cases, the patient was on DRV at time of death in the former, and had discontinued DRV two weeks prior to death in the latter due to the physician's decision. One new SAE was reported in this group this year, a case of spastic diplegia and categorised as serious, the date of event was unknown with no date of resolution given, the patient remained on DRV at last visit.

CHMP's comments:

In the period covered by this last report, no adverse events have been reported for licensed doses of darunavir. However, three patients who received unlicensed doses experienced non-serious adverse events including rash, gastrointestinal symptoms and raised triglycerides levels. All three patients remained on darunavir despite the adverse events.

In the five-year period of this study, a total of 534 HIV-1 infected children and adolescents were exposed to darunavir in this study. Clinical data were available for 383 out of 534 children. In this five-year period, 11 out of 383 participants for whom the clinical data were available, reported one or more adverse events that were considered to be causally related to darunavir. The reported adverse events in these patients constituted known and listed events such as raised triglycerides, rash, and abdominal pain. There was no difference in the pattern of observed adverse events between the patients on the licensed b.i.d. dose, licensed 800mg q.d dose or unlicensed doses.

Discontinuations

Eighty-four of the 531 patients (16%) were not on DRV at their last follow-up visit.

This proportion is slightly higher than the 11% (48/431) reported to have discontinued in last year's report. Of the 129 patients on the licensed b.i.d. dose, 33 (26%) discontinued DRV at last visit, of whom 9 discontinued <6 months after start of DRV, 4 patients after 6-<12 months, 17 patients ≥12 months and 3 at an unknown duration. The reasons given for stopping were: treatment failure (3); adverse events – death (1, HIV-related metastatic adenocarcinoma, DRV associated causality unknown), lipodystrophy (1), dyslipidaemia (2), toxicity (1) drug interaction (1); patient-related reasons – non-compliance (2), patient's wish/decision (4); structured treatment interruption (1); physician's decision (2), other causes (8) and unknown (7).

Twenty-five (12%) of the 216 patients on the licensed 800mg q.d. dose stopped a DRV-containing regimen due to treatment failure (1), adverse events (4, including one death – due to a non-AIDS defining cancer, causality to DRV unknown), patient-related reasons (8), physician related reason (8) and other/unknown reasons (4).

Five (7%) of the 75 patients on an unlicensed dose of DRV at start of treatment discontinued treatment due to: treatment failure (3), death (1, an AIDS defining event, not related to DRV), and for unknown reasons (1). There were no treatment discontinuations in the 0-<3 years group nor in the patient aged 3-<12 years on a DRV q.d dose.

Of the 107 patients with missing weight/dose data, 21 (20%) patients reported to have stopped taking DRV. The reasons for discontinuations were: death (1 – death due to invasive bacterial infection,

causality unknown), toxicity (2), patient-related reasons (6), simplified treatment available (3) and other/unknown reasons (9).

Table 5 Reasons for discontinuation of DRV

	Treatment status (n (%))					
	Aged 3-<18 years on licensed b.i.d dose (n=129)	Aged 12-<18 years on licensed 800mg q.d dose (n=216)	Aged 3-<18 years only ever on unlicensed dose (n=75)	Age 0-<3 years (n=3)	Missing weight or dose (n=107)	Total (n=530)*
Total not on DRV at last follow-up	**33 (26)**	**25 (12)**	**5 (7)**	**(0)**	**21 (20)**	**84 (16)**
Time to discontinuation:						
<1 month	3 (9)	4 (16)	0 (0)	0 (0)	2 (10)	9 (11)
1 - <6 months	6 (18)	5 (20)	0 (0)	0 (0)	5 (24)	16 (19)
6 - <12 months	4 (12)	4 (16)	2 (40)	0 (0)	4 (19)	14 (17)
≥12 months	17 (52)	12 (48)	3 (60)	0 (0)	9 (43)	41 (49)
Unknown	3 (9)	0 (0)	0 (0)	0 (0)	1 (5)	4 (5)
Reasons for stopping DRV:						
Treatment failure	3 (9)	1 (4)	3 (60)	0 (0)	0 (0)	7 (8)
Adverse events						
Death	1 (3)	1 (4)	1 (20)	0 (0)	1 (5)	4 (5)
Toxicity	1 (3)	2 (8)	0 (0)	0 (0)	2 (10)	5 (6)
Drug interaction	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Dyslipidaemia	2 (6)	1 (4)	0 (0)	0 (0)	0 (0)	3 (4)
Lipodystrophy	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Patient-related						
Non-compliance	2 (6)	4 (16)	0 (0)	0 (0)	3 (14)	9 (11)
Patient's wish/decision	4 (12)	4 (16)	0 (0)	0 (0)	3 (14)	11 (13)
Physician related						
Physician's decision	2 (6)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)
Simplified treatment available	0 (0)	8 (32)	0 (0)	0 (0)	3 (14)	11 (13)
Structured Treatment Interruption	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Other causes	8 (24)	3 (12)	0 (0)	0 (0)	1 (5)	12 (14)
Unknown	7 (21)	1 (4)	1 (20)	0 (0)	8 (38)	17 (20)

CHMP's comment:

A slightly higher proportion of the patients have discontinued darunavir in the last year of the study as compared to the previous year (13% vs. 11%). In the five-year period of the study, a total of 84 patients (16%) have discontinued darunavir. The most common reasons for discontinuation in these 84 patients were the patient's wish/decision, non-compliance and the availability of another simplified ART regimen. The other reasons for discontinuation represented isolated events and their review did not reveal new important safety information.

Context data

The UK/Ireland cohort is the largest of the participating cohorts, with 883 patients aged <18 years in current follow-up. The Italian, Spanish, Russian and Thai cohorts have 444, 376, 279 and 265 patients aged <18 years in current follow-up respectively. Among those on current follow up, 1871 patients have a HCV serostatus reported, of whom 71 were seropositive, giving an overall prevalence of 3.4%. The largest number of HCV seropositive patients were reported by the Russian cohort (34, giving a seroprevalence of 12%) followed by the Thai and Spanish cohorts (n=12 and n=7 respectively). Overall 33% of patients aged <18 years and in current follow-up were taking a 3-drug NNRTI-based regimen, and 40% a boosted PI-based regimen. The proportion of each cohort not currently on ART varied from 0% to 22%.

It is not possible to estimate the coverage of the EPPICC paediatric cohorts, in terms of the number of children included in these cohorts compared to the number infected as a whole in the countries represented. This is due to a wide variation in the quality of the surveillance systems used in these countries, making national estimates, and comparisons of estimates between countries, unreliable.

Only two contributing cohorts have nationwide data capture: the Collaborative HIV Paediatric Study follows virtually all HIV-infected children receiving treatment in the UK and Ireland, and contributed 45% of the total number of patients to this analysis; and the Italian Register has >100 collaborating clinics and contributed 11% of patients.

However the context data provided indicate that the cohorts together had 3,115 patients in current follow-up aged <18 years. Within these cohorts, 531 patients aged <18 years had ever taken DRV, this is an increase of 100 patients from the 431 patients reported last year, although our network has expanded this year with the addition of two new countries (Netherlands and Latvia, contributing 14 patients ever received DRV).

While the use of DRV has increased steadily over the course of this 5-year study, it remains relatively infrequently used in paediatric patients in Europe, with around 17% (531/3115) of paediatric patients having ever taken it. However, at last follow-up, boosted PI+NRTI based regimens were the most common ART regimens taken, with approximately 40% of cohort patients on ART taking this type of regimen. Pharmacovigilance data suggest that 262 paediatric patients taking DRV since 1st January 2011 were on DRV at last follow-up, and that these children constitute 21% (262/1225) of all patients on boosted PI+NRTI based regimens.

CHMP's comments:

The context data suggest that DRV remains to be relatively infrequently prescribed to children compared to other ART agents – with around 17% of HIV-infected children (531 on DRV-containing ART out of 3115 on any ART) in the contributing cohorts had ever taken any dose of DRV. This could be explained by the fact that darunavir has been recently approved for treatment of younger children and therefore not much used in this group. Furthermore, other PI's are preferred in children < 12 years old according to the current PENTA guidelines.[1]

MAH conclusion

Laboratory abnormalities and adverse events were reported infrequently, and only ten patients had adverse events considered by the treating physician to be causally related to DRV. Since DRV must be taken with ritonavir and other antiretroviral drugs (and in some cases with concomitant medication), it is difficult to attribute causality for these occurrences to any one specific agent. DRV was prescribed relatively infrequently in the paediatric HIV-infected population.

In summary, results from this five year pharmacovigilance study, which include cohorts across 16 countries, suggest that in general, DRV-containing regimens, both licensed and unlicensed, appear to be well tolerated in the paediatric population of HIV-infected patients, and that discontinuations for adverse events were rarely reported.

[1] [1]A. Bamford et al 2015 *HIV Medicine*. Paediatric European Network for Treatment of AIDS (PENTA) guidelines for treatment of paediatric HIV-1 infection 2015: optimizing health in preparation for adult life

3. CHMP's overall conclusion and recommendation

FUM 051 Pharmacovigilance study to define the long-term safety profile of darunavir/ritonavir in HIV-1-infected children and adolescents in Europe

Overall Conclusion:

Based on the review of the *fifth, final Annual Report "Pharmacovigilance study on the safety and use of darunavir (DRV) in HIV infected children and adolescents in Europe"* regarding FUM 051 (EMEA/H/C/000707/FUM) for Prezista (darunavir), the CHMP concludes the following:

- The number of children and adolescents participating in the study has increased from 123 patients in the first year (2011) of the study to 531 in the fifth, final year. Despite of this increase, the children who received darunavir for the first time when they were under the age of 12 are less represented in the study population. The largest proportion of children received darunavir for the first time when they were 12-<18 year old (422, 79%), while a smaller proportion of children received darunavir for the first time when they were < 12 years old (109/531, 21%) with the smallest proportion of children under the age of 6 (11, 2%).

  The small number of children below 12 years old, and especially below 6 years could be explained by the fact that darunavir was indicated in older children for a longer period of time and the indication in children < 6 years old was granted only in 2014. In addition, in the current clinical guidelines for treatment of HIV infected children in Europe (*i.e.,* PENTA guidelines 2015) , use of darunavir-containing ART regimens is recommend in children > 12 years old, while other protease inhibitors are recommended in children below 12 years old.

- Overall, in the course of this 5-year study, no new safety information with regard to long-term safety in children and adolescents became available. In the five-year period of this study, a total of 531 HIV-1 infected children and adolescents were exposed to darunavir. In this five-year period, 11 out of 383 participants for whom the clinical data were available, reported one or more adverse events that were considered to be causally related to darunavir. The reported adverse events in these 11 patients constituted known and listed events such as raised triglycerides, rash, and abdominal pain. There was no difference in the pattern of observed adverse events between the patients on the licensed b.i.d. dose, licensed 800mg q.d dose or unlicensed doses. However, considering the low number of children who received darunavir first time when they were under the age of 6, no firm conclusions could be drawn regarding this age group.

- Based on the results of the study, the long-term safety of darunavir in children aged from 6 to 17 years old is no longer considered missing information (per EU-RMP of Prezista) and could be removed from the RMP. Long-term safety of darunavir in children from 3 to 6 years old is still considered as missing information and is subject to routine monitoring and discussion of any new data in the future PSURs.

- In conclusion, the FUM 051, Pharmacovigilance study to define the long-term safety profile of darunavir/ritonavir in HIV-1-infected children and adolescents in Europe, is considered fulfilled. The safety concern (as missing information) "long-term safety in children 3-17 years old" should be adjusted to "long term safety in children 3-<6 years old".

☒ Fulfilled:

- The FUM 051, Pharmacovigilance study to define the long-term safety profile of darunavir/ritonavir in HIV-1-infected children and adolescents in Europe, is considered fulfilled. The MAH should update the RMP to update the completion of the study and to adjust the safety concern (as missing information in the RMP) "long-term safety in children 3-17 years old" to "long term safety in children 3-<6 years old". This should be done at the time of the next RMP update for Prezista.

4. Additional clarification requested

None