25 April 2014
EMA/339053/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Telzir

International non-proprietary name: FOSAMPRENAVIR

Procedure No. EMEA/H/C/000534/II/0074

Note

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

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, ViiV Healthcare submitted to the European Medicines Agency on 18 December 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Telzir	FOSAMPRENAVIR	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

The MAH proposed to include in SmPC sections 4.8 and 5.1 updated information on safety, antiviral response and treatment resistance in HIV-1 infected paediatric subjects, based on results of studies previously submitted as post-authorisation measures. In addition, the Product information is updated to the latest QRD template version and editorial changes are implemented in SmPC sections 4.4, 4.8 and 5.1.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Rapporteur: Joseph Emmerich

1.2. Steps taken for the assessment

Submission date:	18 December 2013
Start of procedure:	24 February 2014
Rapporteur's assessment report circulated on:	28 March 2014
CHMP opinion:	25 April 2014

2. Scientific discussion

2.1. Introduction

Telzir (fosamprenavir, FPV) is available as 700 mg film-coated tablets and 50 mg/mL oral suspension and is approved for the treatment of HIV infection in patients 6 years old and above, in combination with low dose ritonavir (RTV) and other antiretrovirals agents.

Three Phase II studies form the basis of the paediatric development programme:

- Study APV29005 evaluates safety, tolerability, PK and antiviral activity of FPV/RTV BID regimens in PI-naïve subjects 2 to <6 years of age and a BID regimen of FPV/RTV in PI-naïve and -experienced subjects 2 to 18 years of age. 48 week CSR has been previously submitted on 08/08/2012 (procedure FUM 048.1).

- Study APV20002 evaluates safety, tolerability, PK and antiviral activity of FPV/RTV BID regimens in subjects aged 4 weeks to <2 years. 48 week CSR has been previously submitted on 08/08/2012 (procedure FUM 048.1).
- Study APV20003 evaluates safety, tolerability, PK and antiviral activity of a once daily regimen of FPV/RTV in PI-naïve and -experienced subjects 2 to 18 years old. 168 week CSR has been previously submitted on 08/06/2009 (procedure P46 060).

While Study APV29005 is considered pivotal, Study APV20003 and Study APV20002 provide supportive safety data. Study APV20003 also contributes to information on resistance.

24-week and 48-week interim data from APV29005, 48-week interim data from APV20002 and 168-week data from APV20003 are available.

This Type II variation application proposed to update information on safety and antiviral response of FPV/RTV in HIV-1 infected paediatric subjects and also to update information on resistance, modifying SmPC Sections 4.8 and 5.1.

Of note, there is no approved Paediatric Investigation Plan (PIP) for Telzir.

2.2. Clinical Efficacy aspects

2.2.1. Methods – analysis of data submitted

The Week 48 results from study APV29005 were proposed as supportive for the changes in Product information. Study APV29005 was a 48 week, phase II, non-comparative, open-label, multi-cohort, multicentre study to evaluate the safety, tolerability, pharmacokinetics and antiviral activity of fosamprenavir/ritonavir BID when administered to HIV-1 infected, PI-naive and experienced, paediatric subjects, 2 to 18 years old and of fosamprenavir BID administered to PI-naive, paediatric subjects 2 to < 6 Years Old.

48 week Clinical Study Report (CSR) has been previously submitted on 08/08/2012 and assessed in procedures for post-authorisation measures FUM 046, FUM 048 and FUM 048.1. The design of the study has been previously discussed also in variation II/0018 (assessment report published), in which week 24 CSR was provided. It could be noted that the APV29005 protocol was later amended to administer FPV/RTV at a dose of 23/3 mg/kg BID for the 2 to 5 year old age group to ensure target exposure is reached.

2.2.2. Results

Baseline characteristics

Baseline characteristics are presented in the tables below.

Table 1. Summary of ART Status and Prior NRTI, NNRTI, and PI Antiretroviral Therapy in APV29005 ITT(E) Population by Age at Entry

	FPV/RTV		
	2 to <6 years N=19	**6 to <12 years N=30**	**12 to 18 years N=40**
ART/PI Status, n(%)			
ART-naïve	7 (37)	2 (7)	14 (35)
ART-experienced/PI-naïve	6 (32)	8 (27)	12 (30)
PI-experienced	6 (32)	20 (67)	14 (35)
Duration of Prior ART			
Any NRTI taken, n (%)	10 (53)	26 (87)	25 (63)
Median duration of all prior NRTI exposure in Weeks (range)	153 (46-288)	386 (1-596)	409 (50-673)
Any NNRTIs taken, n (%)	8 (42)	17 (57)	15 (38)
Median duration of all prior NNRTI exposure in Weeks (range)	56 (0-160)	125 (28-274)	150 (8-304)
Any PI taken, n (%)	6 (32)	19 (63)	14 (35)
Median duration of all prior PI exposure in Weeks (range)	142 (48-288)	253 (27-423)	209 (50-434)

Table 2. Distribution of Plasma HIV-1 RNA Values and CD4+ Cell Counts at Baseline for APV29005 ITT(E) Population by Treatment and Age Group

	FPV/RTV			
	2 to <6 years N=19	**6 to <12 years N=30**	**12 to 18 years N=40**	**Total N=89**
Baseline HIV-1 RNA, n	19	29	40	88
Median plasma HIV-1 RNA log_{10} copies/mL, (IQR)	4.7 (4.4, 5.3)	4.6 (4.1, 5.1)	4.7 (4.1, 5.2)	4.7 (4.2, 5.2)
HIV-1 RNA copies/mL, n (%)				
400-<5000	1 (5)	5 (17)	4 (10)	10 (11)
5000-<100,000	11 (58)	15 (52)	23 (58)	49 (56)
100,000-<250,000	4 (21)	7 (24)	8 (20)	19 (22)
250,000-<500,000	1 (5)	2 (7)	2 (5)	5 (6)
≥500,000	2 (11)	0	3 (8)	5 (6)
BaselineCD4+ cell counts (absolute), n	19	30	40	89
Median CD4+ cells/mm³ (IQR)	915 (608, 1160)	470 (290, 720)	250 (100, 397)	410 (200, 680)
CD4+ cells/mm³, n (%)				
<100	0	0	8 (20)	8 (9)
100-<200	0	4 (13)	10 (25)	14 (16)
200-<350	0	6 (20)	9 (23)	15 (17)
350-<500	2 (11)	8 (27)	7 (18)	17 (19)
≥500	17 (89)	12 (40)	6 (15)	35 (39)
Baseline % CD4+ cells, n	19	30	40	89
Median % CD4+ cells (IQR)	26 (21, 30)	25 (15, 30)	15 (9, 29)	21 (12, 29)
% CD4+ cells, n (%)				
<15	1 (5)	7 (23)	20 (50)	28 (31)
15-<25	7 (37)	8 (27)	9 (23)	24 (27)
25-<50	11 (58)	13 (43)	11 (28)	35 (39)
≥50	0	2 (7)	0	2 (2)

Antiviral response

Summary of antiviral response is presented below.

Table 3. Proportion of Subjects with Plasma HIV-1 RNA <400 copies/mL by Visit and Age Group at Entry in APV29005 ITT(E) Population (MSD=F)

	FPV/RTV		
Actual Relative Time	**2 to <6 years N=19 n/N (%)**	**6 to <12 years N=30 n/N (%)**	**12 to 18 years N=40 n/N (%)**
Baseline	0/19	0/30	0/40
Week 2	2/19 (11)	5/30 (17)	7/40 (18)
Week 4	6/19 (32)	8/30 (27)	17/40 (43)
Week 8	10/19 (53)	10/30 (33)	22/40 (55)
Week 12	13/19 (68)	14/30 (47)	27/40 (68)
Week 16	13/19 (68)	15/30 (50)	21/40 (53)
Week 24	16/19 (84)	16/30 (53)	25/40 (63)
Week 36	14/19 (74)	13/30 (43)	22/40 (55)
Week 48	14/19 (74)	16/30 (53)	25/40 (63)

Immunological response

The median change in percent CD4+ cell count from baseline showed improvements in all age groups ranging from 7% in children 6 to <12 and 12 to <18 years to 10% in children aged 2 to <6 years receiving FPV/RTV.

Resistance

Week 48 results from study APV29005 and results up to Week 108 from Study APV20003 were regarded as supportive for the proposed changes.

Among the 81 PI-naïve patients treated with FPV/RTV, 15 paediatric patients met study-defined virological failure. Treatment-emergent major or amprenavir (APV)-associated protease mutations were observed in virus isolated from 2 treatment-experienced but PI-naïve patients. The viral resistance patterns were similar to those observed in treatment-experienced but PI-naïve HIV-infected adults.

Among the 77 PI-experienced patients treated with FPV/RTV, 43 paediatric patients met study-defined virological failure. Treatment-emergent major or amprenavir (APV)-associated protease mutations were observed in virus isolated from 7 patients. The viral resistance patterns were similar to those observed in treatment-experienced HIV-infected adults.

2.2.3. Discussion

The youngest cohort (2 to <6 years) concerns subjects for whom the use of Telzir is not currently approved. Therefore, the efficacy results in this cohort are not discussed in more details.

The ART/PI status was different according to cohorts (more PI-experienced patients aged from 6 to <12years and more ARV-naïve patients aged from 12 to <18 years). At baseline, subjects aged from 12 to <18 years had similar viral load but a lower CD4 cells count, reflecting a longest evolution of disease.

In both cohorts, similar efficacy results were obtained through 24-weeks and 48-weeks of treatment.

Compared to 24-weeks results (as summarized in the current SmPC), the median increase in CD4+ cell count from baseline is higher at week 48 (10% in the PI-naïve subjects and 6% in the PI-experienced subjects vs. respectively 8% and 4% at Week 24), reflecting an adequate long term antiviral activity of Telzir in this population.

As expected, the rate of virological failures is higher in PI-experienced subjects (56%) than PI-naïve subjects (19%). The mutational profile is similar between children and adults.

2.3. Clinical Safety aspects

2.3.1. Methods – analysis of data submitted

An integrated analysis of safety data for the FPV/RTV treatment groups from APV29005 (Week 24) and APV20003 (final data, Week 168) was completed in 2011 to provide a larger safety database across all studied age groups and increase the ability to detect small safety signals. Since this analysis, in addition 48 week data for studies APV29005 and APV20002 have become available.

2.3.2. Results

Integrated safety data from APV29005 and APV20003

AEs regardless of causality

Reported AEs regardless of causality are summarised below.

Table 4. Summary of Common Adverse Events by System Organ Class and Age at Entry in at least 10% of Subjects in Any of the Age Groups for Integrated Safety Analysis of Studies APV29005 and APV20003

	Number (%) of Subjects APV29005 and APV20003 integrated FPV/RTV		
Adverse Event	**2 to <6 years (N=36)**	**6 to <12 years (N=47)**	**12 to 18 years (N=75)**
Any Event	35 (97)	42 (89)	72 (96)
Infections and Infestations	27 (75)	34 (72)	53 (71)
Upper respiratory tract infection	13 (36)	9 (19)	14 (19)
Nasopharyngitis	7 (19)	12 (26)	8 (11)
Bronchitis	4 (11)	6 (13)	14 (19)
Rhinitis	10 (28)	1 (2)	5 (7)
Otitis media	7 (19)	7 (15)	4 (5)
Ear infection	2 (6)	7 (15)	4 (5)
Influenza	2 (6)	6 (13)	0
Gastrointestinal	27 (75)	32 (68)	46 (61)
Vomiting	13 (36)	22 (47)	21 (28)
Diarrhoea	6 (17)	12 (26)	26 (35)
Nausea	3 (8)	2 (4)	21 (28)
Abdominal pain[a]	6 (17)	4 (9)	11 (15)
Dental caries	4 (11)	3 (6)	2 (3)
Respiratory, thoracic and mediastinal	18(50)	21 (45)	35 (47)
Cough	13 (36)	14 (30)	22 (29)
Oropharyngeal pain	0	4 (9)	10 (13)
Skin and subcutaneous tissue	14 (39)	16 (34)	26 (35)
Rash	8 (22)	6 (13)	9 (12)
Acne	0	1 (2)	8 (11)
General disorders and administration site conditions	6 (17)	20 (43)	19 (25)
Pyrexia	4 (11)	16 (34)	12 (16)
Nervous system	4 (11)	11 (23)	21 (28)
Headache	4 (11)	9 (19)	19 (25)

a. Includes abdominal pain and abdominal pain upper.

Vomiting was most frequent in the 2 to <6 years and 6 to <12 years age groups, and was seen to a lesser extent in the 12 to 18 years age group, many of whom took tablets rather than the suspension. Nausea was more frequently reported in the 12 to 18 year age group than the younger age groups and diarrhoea and headache were more frequently reported in the older two age groups compared to the 2 to <6 year olds. Upper respiratory tract infection and rhinitis were more commonly reported in the 2 to <6 years age group than in the older age groups, reflecting the common illnesses/viral infections experienced in younger children.

Drug-related AEs

Table 5. Summary of Drug-Related Adverse Events by Age in More Than One Subject in Any Age Group for Integrated Safety Analysis of Studies APV29005 and APV20003

	Number (%) of Subjects		
	APV29005 and APV2003 integrated FPV/RTV		
Drug-Related Adverse Event	**2 to <6 years (N=36)**	**6 to <12 years (N=47)**	**12 to 18 years (N=75)**
Any Event	14 (39)	17 (36)	37 (49)
Vomiting	8 (22)	13 (28)	10 (13)
Nausea	2 (6)	0	18 (24)
Diarrhoea	1 (3)	1 (2)	14 (19)
Hypertriglyceridemia[a]	2 (6)	1 (2)	2 (3)
Rash	0	3 (6)	2 (3)
Hypercholesterolemia[b]	3 (8)	0	1 (1)
Abdominal pain[c]	1 (3)	0	3 (4)
Flatulence	0	1 (2)	3 (4)
Headache	0	1 (2)	3 (4)
Parasthesia oral	0	0	3 (4)
Lipodystrophy acquired	0	0	2 (3)
Lipohypertrophy	0	0	2 (3)

a. Includes events under the preferred terms 'hypertriglyceridemia' (reported under Metabolism and Nutrition Disorders system organ class) and 'blood triglycerides increased'
b. Includes events under the preferred terms 'hypercholesterolemia' (reported under Metabolism and Nutrition Disorders system organ class) and 'blood cholesterol increased'
c. Includes abdominal pain and abdominal pain upper

Vomiting was more frequently reported in the 2 to <6 years and 6 to <12 years age groups and nausea and diarrhoea were more frequently reported in the 12 to 18 years age group.

Serious AEs and deaths

Table 6. Summary of Serious Adverse Events by Age at Entry in More Than One Subject in Age Group for Integrated Safety Summary of Studies APV29005 and APV20003

	Number (%) of Subjects		
	APV29005 and APV20003 integrated FPV/RTV		
Serious Adverse Event	**2 to <6 years (N=36)**	**6 to <12 years (N=47)**	**12 to 18 years (N=75)**
Any Event	9 (25)	7 (15)	15 (20)
Drug hypersensitivity[a]	3 (8)	2 (4)	4 (5)
Pneumonia	2 (6)	1 (2)	0
Measles	1 (3)	0	2 (3)

a. All cases were attributed to abacavir

Two SAEs, reported in APV29005 for the same patient at different time points, were considered by the investigator to be drug-related. The events were (1) adverse drug reaction described as rash/fever/headache/swollen lips, and (2) drug hypersensitivity reported at this time by the investigator as an abacavir hypersensitivity reaction.

The frequency of SAEs was similar across age groups but numbers were small.

There were no deaths reported in APV29005 or APV20003.

Grade 3/4 laboratory abnormalities

Table 7. Summary of Treatment-Emergent Grade 3/4 Laboratory Toxicities in More Than One Subject in Any Age Group for Integrated Safety Analysis of FPV/RTV for Studies APV29005 and APV20003

	APV29005 and APV20003 integrated FPV/RTV		
	n/N (%)		
Laboratory Parameter	2 to <6 years (N=36)	6 to <12 years (N=47)	12 to 18 years (N=75)
Clinical Chemistry:			
All Parameters of Special Interest	4/35 (11)	8/44 (18)	6/74 (8)
Alanine aminotransferase	0/35	1/44 (2)	3/74 (4)
Aspartate aminotransferase	0/35	2/44 (5)	3/74 (4)
Total cholesterol	0/35	3/42 (7)	0/73
LDL cholesterol	4/35 (11)	4/42 (10)	0/73
Lipase	0/35	0/42	0/72
Triglycerides	0/35	0/42	1/73 (1)
Hyperglycaemia	0/35	0/44	0/74
All Other Parameters	3/35 (9)	5/44 (11)	5/74 (7)
Haematology:			
All Parameters	5/34 (15)	7/43 (16)	11/74 (15)
Neutropenia	4/34 (12)	7/43 (16)	9/73 (12)
Thrombocytopenia	1/34 (3)	0	2/74 (3)

The majority of subjects had hepatic transaminase, bilirubin, and lipase values that were below the level of clinical concern throughout the study period.

Five percent (8/150) of subjects had Grade 3 LDL cholesterol. Increased lipids were rarely treatment-limiting; however, two subjects (who were receiving FPV/RTV in Study APV20003) discontinued therapy because of hypertriglyceridemia.

In study APV29005, Grade 3/4 neutropenia was reported in 15/104 subjects (14%). Most of the subjects (n=14) had one event of neutropenia or two events with normal values in between. Thirteen of the 15 cases were taking concomitant ART medications (zidovudine or stavudine) or trimethoprimsulfamethoxazole which may have contributed to the neutropenia.

In study APV20003, Grade 3/4 neutropenia was documented more frequently (20%, 13/66) than in Study APV29005. Neutropenia occurred in all age cohorts, in subjects ranging from 3 to 15 years of age, and in both males and females. Most cases of neutropenia occurred as isolated instances, but 77% (10/13) of subjects had at least one other episode of at least Grade 1 neutropenia. There was no evidence of downward trends in the neutrophil values during the study. The reason for the frequency of neutropenia is unclear, and confounded by several factors, including concomitant medications, possible sample degradation and a change in the DAIDS toxicity gradings.

Week 48 safety data from APV29005 and APV20002

AEs regardless of causality

Table 8. Summary of Common Adverse Events by System Organ Class in at least 10% of Subjects in APV29005 or APV20002 – Safety Populations

	Number (%) of Subjects	
	APV29005	APV20002
Adverse Event	**(N=89)**	**(N=59)**
Any Event	83 (93)	54 (92)
Infections and Infestations		
Upper respiratory tract infection	20 (22)	21 (36)
Nasopharyngitis	16 (18)	17 (29)
Rhinitis	15 (17)	15 (25)
Bronchitis	12 (13)	7 (12)
Ear infection	11 (12)	0
Otitis media	10 (11)	16 (27)
Pharyngitis	8 (9)	17 (29)
Tonsillitis	5 (6)	10 (17)
Otitis media acute	3 (3)	7 (12)
Impetigo	2 (2)	7 (12)
Bronchiolitis	0	6 (10)
Gastrointestinal		
Vomiting	28 (31)	13 (22)
Diarrhoea	26 (29)	32 (54)
Nausea	10 (11)	1 (2)
Gastroenteritis		21 (36)
Respiratory, Thoracic and Mediastinal		
Cough	33 (37)	10 (17)
Rhinorrhoea	10 (11)	2 (3)
Oropharyngeal pain	9 (10)	0
Skin and Subcutaneous Tissue		
Rash[a]	14 (16)	5 (8)
Eczema	3 (6)	6 (10)
Seborrhoeic dermatitis	1 (1)	7 (12)
Dermatitis diaper	0	7 (12)
General Disorders and Administration Site Conditions		
Pyrexia	20 (22)	4 (7)
Investigations		
Hypercholesterolemia[b]	3 (3)	11 (19)
Nervous System		
Headache	14 (16)	0
Eye Disorders		
Conjunctivitis	3 (6)	10 (17)

a. 'Rash' preferred term only.
b. Includes events under the preferred terms 'hypercholesterolemia' and 'blood cholesterol increased'

Drug-related AEs

Table 9. Summary of Drug-Related Adverse Events by Frequency in More Than One Subject in Studies APV29005 or APV20002 – Safety Population

	Number (%) of Subjects	
	APV29005	APV20002
Drug-Related Adverse Event	(N=89)	(N=59)
Any event		
Vomiting	13 (15)	2 (3)
Diarrhoea	9 (10)	4 (7)
Nausea	6 (7)	0
Rash	3 (3)	0
Flatulence	2 (2)	0
Headache	2 (2)	0
Abdominal pain[a]	2 (2)	0
Hypertriglyceridemia[b]	1 (1)	4 (7)
Hypercholesterolemia[c]	1 (1)	9 (16)
Gastroenteritis	0	2 (3)

a. Includes abdominal pain and abdominal pain upper.
b. Includes events under the preferred terms 'hypertriglyceridemia' and 'blood triglycerides increased'
c. Includes events under the preferred terms 'hypercholesterolemia' and 'blood cholesterol increased'

Serious AEs and deaths

Drug hypersensitivity was the most frequent SAE in APV29005, but was not reported by any subjects in APV20002. The most frequent SAEs reported in APV20002 were pneumonia, gastroenteritis and bronchopneumonia.

Three deaths were reported in Study APV20002:

- A 24-month-old male died 12 days after a single dose of FPV and 11 days after a single dose of FPV/RTV. The investigator reported that the subject died due to an acute abdominal disorder with acute abdominal pain and vomiting of unknown aetiology as secondary events. The investigator did not consider the event to be related to the investigational products.
- A fatal outcome occurred in a 19-month-old female on Day 85 of the study. The subject experienced Grade 4 septicaemia and died despite resuscitation. The investigator did not consider the event to be related to the investigational products. The fatal AE of septicaemia for this subject does not appear in the AE summary tables as the last dose of investigational product was taken the day before the event occurred.
- A Grade 4 gastroenteritis and poisoning from a traditional herbal medicine occurred in a 2-month-old male subject. The AE was reported as starting on 03 March 2009 (Study Day 6). The traditional herbal medicine was administered 3 days before the events while FPV, RTV and abacavir (ABC) were initiated 7 days before the events. The subject had presented to a local clinic on 04 Mar 2009, the day before the death, with a history of diarrhoea and was asked to return the next day. Hospital records indicated a history of diarrhoea, vomiting, cough and shortness of breath. On admission, the child was acutely ill and died later that day, on 05 Mar 2009. The investigator considered that there was a reasonable possibility that the acute gastroenteritis may have been caused by FPV and RTV and that there was no reasonable possibility that the traditional herbal medicine poisoning may have been caused by FPV and RTV. The death certificate cited 'death from natural causes'.

Grade 3/4 laboratory abnormalities

Table 10. Summary of Treatment-Emergent Grade 3/4 Laboratory Toxicities in More Than One Subject in Studies APV29005 and APV20002 – Safety Population

Laboratory Parameter	N	APV29005 (N=89) n/N (%)	N	APV20002 (N=59) n/N (%)
Clinical Chemistry:				
All Parameters	87	17 (20)	51	10 (20)
All Parameters of Special Interest	87	9 (10)	51	3 (6)
Alanine aminotransferase	87	2 (2)	51	3 (6)
Aspartate aminotransferase	87	2 (2)	51	0
Total cholesterol	43	2 (5)	49	0
LDL cholesterol	43	4 (9)	49	0
Lipase	85	0	10	0
Triglycerides	43	0	49	0
Hyperglycaemia	58	0	51	0
Haematology:				
All Parameters	85	8 (9)	51	6 (12)
Neutropenia	84	7 (8)	51	5 (10)
Thrombocytopenia	85	1 (1)	51	0
Haemoglobin	85	0	51	1 (2)

In APV20002, all five neutropenia cases resolved with continued FPV treatment.

2.3.3. Discussion

Integrated safety data from APV29005 and APV20003

No new safety concerns have been identified in the integrated safety data.

Although vomiting was more observed in the youngest subjects (receiving oral solution) than the older cohort (most of them receive tablet formulation), the rate of combined upper gastrointestinal disorders (vomiting + nausea) was similar between the three cohorts.

Diarrhoea was very common (19%) in 12 to 18 years old subjects, as mentioned in the current SmPC of Telzir. Only two cases of diarrhoea (2%) were considered drug-related in the youngest cohort, whereas 18 cases (22%) were initially observed. However, it may be more difficult to impute Telzir as the cause of these diarrhoeas in the younger patients.

Rash was reported, but is a known common adverse reaction of Telzir. Increased of ALAT/ASAT and cholesterol levels are also known common adverse reactions of Telzir.

Neutropenia was commonly reported, but not considered drug-related and is probably due to concomitant medications (for example, 42% of subjects included in the study APV29005 received sulfamethoxazole + trimethoprim).

Week 48 safety data from APV29005 and APV20002

Like in the integrated safety data from studies APV29005 and APV20003, vomiting and diarrhoea were the most common AEs. Metabolic disorders (hypertriglyceridemia and hypercholesterolemia) were also frequently observed, which is in accordance to the known safety profile of Telzir.

Given the sequence of events, the death reported in 2-month-old male subject could be related to the gastroenteritis, which could be induced by Telzir and/or traditional herbal medicine. The role of Telzir in this death cannot be ruled out.

Similarly as in the integrated safety data from studies APV29005 and APV20003, neutropenia cases are probably due to concomitant medications, and resolved without discontinuation of Telzir. No new laboratory abnormalities were observed.

2.4. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed:

4.8 Undesirable effects

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Paediatric / other populations

Children and adolescents: The adverse reaction profile in children and adolescents is based on integrated safety data from two studies (APV29005 Week 24 data and APV20003 Week 168 data [final data]) in which ~~126~~ 158 HIV-1 infected subjects 2 to 18 years of age received fosamprenavir with ritonavir with background nucleoside reverse transcriptase inhibitor therapy (see section 5.1 for information on dosing regimens applied for each age group). 79~~70~~ % of subjects received greater than 48 weeks of exposure.
Overall the safety profile in these 158~~126~~ children and adolescents was similar to that observed in the adult population. Vomiting occurred more frequently amongst paediatric patients. Drug-related adverse reactions were more common in APV20003 (~~55~~57%) where subjects received once daily fosamprenavir / ritonavir when compared to APV29005 (33~~39~~%) where subjects received twice daily fosamprenavir / ritonavir.
No new safety concerns were identified from analyses of 48 week data from studies APV29005 or APV20002, in which 54 subjects 4 weeks to <2 years of age received twice daily fosamprenavir / ritonavir with background nucleoside reverse transcriptase inhibitor therapy and 5 subjects received only single doses of fosamprenavir with or without ritonavir.

5.1 Pharmacodynamic properties

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Resistance

In vivo

a) ART-naïve or PI-naïve patients

Various regimens have been assessed in the amprenavir/fosamprenavir development programs with and without co-administration of ritonavir. Analysis of the virological failure samples across these regimens defined four main resistance pathways: V32I+I47V, I50V, I54L/M and I84V. Additional mutations observed which may contribute to resistance were: L10V/F/R, I13V, K20R/T, L33F/V, M36I, M46I/L, I47V/L Q58E, I62V, L63P, V77I, I85V, and I93L.

When ART naïve adult patients were treated with the currently approved doses of fosamprenavir / ritonavir, as for other ritonavir boosted PI regimens, the mutations described were infrequently observed. Sixteen of 434 ART-naïve patients who received fosamprenavir 700mg/ritonavir 100mg twice daily in ESS100732 experienced virological failure by Week 48 with 14 isolates genotyped. Three of 14 isolates had protease resistance mutations. One resistance mutation was observed in each of 3 isolates: K20K/R, I54I/L and I93I/L respectively

~~Genotypic analysis of isolates from 13 of 14 paediatric patients exhibiting virological failure among the 59 PI naïve patients enrolled, demonstrated resistance patterns similar to those observed in adults.~~Among the 81 PI-naïve paediatric patients treated with fosamprenavir / ritonavir, 15 patients met protocol-defined

virological failure through 48 weeks in APV29005 and up to 108 weeks in APV20003. Treatment-emergent major or APV-associated protease mutations were observed in virus isolated from 2 patients. Resistance patterns were similar to those observed in adults.

b) PI-experienced patients

Amprenavir

In the studies of PI-experienced adult patients, PRO30017 (amprenavir 600 mg / ritonavir 100 mg twice daily in sub-study A and B with 80 and 37 patients respectively), the following mutations emerged in patients with virological failure: L10F/I/V, V11I, I13V, K20R, V32I, L33F, E34Q, M36I, M46I/L, I47V, G48V, I50V, I54L/M/T/V, Q58E, D60E, I62V, A71V, V77I, V82A/I, I84V, I85V, L90M and I93L/M.

Fosamprenavir

In the studies of PI-experienced adult patients, APV30003 and its extension, APV30005 (fosamprenavir 700 mg / ritonavir 100 mg twice daily: n=107), the following mutations emerged in patients experiencing virological failure through 96 weeks: L10F/I, L24I, V32I, L33F, M36I, M46I/L, I47V, I50V, I54L/M/S, A71I/T/V, G73S, V82A, I84V, and L90M.

~~In the paediatric studies APV20003 and APV29005, 67 PI-experienced patients were treated with fosamprenavir / ritonavir and of 22 virological failure isolates genotyped, nine patients were found with treatment-emergent protease mutations.~~In the paediatric studies APV20003 and APV29005, 77 PI-experienced patients were treated with fosamprenavir / ritonavir-based regimens and 43 patients met study-defined virologic failure criteria through 48 weeks in APV29005 and up to 108 weeks in APV20003. Treatment-emergent major protease or APV-associated mutations were observed in virus isolated from 1 patient in APV29005 and 6 patients from APV20003. The mutational profiles were similar to those described for PI-experienced adults treated with fosamprenavir / ritonavir.

Antiviral activity according to genotypic/phenotypic resistance

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Children and adolescent patients above the age of six

Fosamprenavir tablets and oral suspension with ritonavir in combination with NRTIs have been evaluated in protease inhibitor naïve and experienced children and adolescent patients. The benefit in this age group has mainly been derived from ~~the ongoing~~ study, APV29005, an open label 48 week study evaluating the pharmacokinetic profiles, safety, and antiviral activity of fosamprenavir with ritonavir administered twice daily to HIV 1 protease inhibitor experienced and naive patients 2 to 18 years of age. Results through ~~24~~ 48 weeks of treatment are provided below.

APV29005 enrolled ~~25~~ 30 patients aged 6 to 11 (the majority of whom were treated with fosamprenavir / ritonavir 18/3 mg/kg twice daily or the adult tablet regimen), and ~~29~~ 40 patients aged 12 to 18 (the majority of whom were treated with the adult tablet regimen). ~~Overall, 27 (50 %) were PI-naïve, 9 of whom were ART-naïve, and 27 (50 %) were PI-experienced. Prior NRTI exposure was extensive, with median durations of 421 and 389 weeks for the PI naïve and experienced patients respectively. The median duration of prior PI exposure was 239 weeks. Overall, patients enrolled with a median 4.6 HIV-1 RNA log10 copies/ml (33 % of whom had > 100,000 copies/ml at baseline) and a median % CD4+ cell of 18 % (37 % of whom had % CD4+ of < 15% at baseline).~~

~~Through 24 weeks of therapy, 70 % (19/27) of protease inhibitor naive and 56 % (15/27) of protease inhibitor experienced patients achieved and maintained a plasma HIV-1 RNA <400 copies/ml (ITT(E), TLOVR). In the ITT(E) population (Observed analysis) at Week 24 the median % CD4+ cell counts increased by 8 % in the PI-naïve subjects and 4 % in the PI-experienced subjects.~~

Table 5. Baseline Characteristics and Efficacy Outcomes at Week 48 in APV29005 ITT(E)

Population

	Patients aged 6 to 11 N=30	Patients aged 12 to 18 N=40
Baseline Characteristics		
ART/PI status, n (%)		
ART-naïve	2 (7)	14 (35)
ART-experienced, PI-naïve	8 (27)	12 (30)
PI-experienced	20 (67)	14 (35)
Median duration of prior ART exposure, weeks		
NRTI	386	409
PI	253	209
Median plasma HIV-1 RNA log10 copies/mL	4.6 (n=29)	4.7
>100,000 copies/ml, n (%)	9 (31)	13 (33)
Median CD4 cells/µl	470	250
CD4 count < 350 cells/µl, n (%)	10 (33)	27 (68)
Efficacy Outcomes		
Patients with plasma HIV-1 RNA <400 copies/ml, Snapshot analysis	16 (53%)	25 (63%)
Median change from baseline in CD4 cells (cells/µl), observed analysis	210 (n=21)	140 (n=35)

During the procedure the CHMP requested that the following proposed change is not included, since the wording affected corresponds to a class labelling for all ARV products and a sufficient justification was not provided to deviate from class wording:

4.8 Undesirable effects

Description of selected adverse reactions

Immune Reactivation Syndrome: in HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported ~~to occur in the setting of immune reactivation~~; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were reviewed and accepted by the CHMP.

In addition, minor editorial changes are implemented in SmPC sections 4.4, 4.8 and 5.1.

3. Overall conclusion and impact on the benefit/risk balance

The changes proposed in the PI are based primarily on integrated safety from Study APV29005 (Week 24 data) and Study APV20003 (Week 168 data), together with Week 48 data from Studies APV29005 and APV20002. These data demonstrate that RTV-boosted FPV was generally well-tolerated in children 4 weeks to 18 years of age. No new safety concerns have been identified since the approval by the European Commission for use of FPV/RTV and other antiretroviral agents for the treatment of HIV infection in children 6 years and above in 2007.

The safety profile in paediatric patients is considered comparable to that of adults although vomiting occurred more frequently amongst paediatric patients. While neutropenia occurred more frequently in paediatric patients, an assessment of the cases suggests that most had a long time to onset and/or were confounded by concomitant, antiretroviral and antibacterial drug treatment commonly associated with neutropenia. Thus, the relationship of neutropenia to FPV use is considered unlikely.

Using the FDA-defined snapshot analysis, proportions of subjects in APV29005 achieving <400 copies/mL at Week 48 were 53% and 63% in the 6-<12 year olds and 12-18 year olds respectively, indicating an adequate antiviral response given that the population included PI-naïve and PI/ART-experienced subjects. An immunologic response, as indicated by increases in absolute CD4+ cell counts was demonstrated. As expected, the rate of virological failures is higher in PI-experienced subjects (56%) than PI-naïve subjects (19%). The mutational profile is similar between children and adults.

The wording added to the SmPC following the analysis of the safety in studies APV29005, APV20003 and APV20002 in children respectively 2 to 18 years of age and 4 weeks to < 2 years of age is acceptable, even if data gathered in the children from 4 weeks to 2 years are very limited. The CHMP also agrees with the proposed update on antiviral activity in children, summarizing results of study APV29005 among subjects from 6 to 18 years old. Of note, results of children < 6 years old are not included since Telzir is not currently approved in this population.

The benefit/risk balance of Telzir is unchanged and still positive. Data from studies APV29005, APV20002 and APV20003 did not identify new safety concerns and new resistance patterns in paediatric subjects. The antiviral activity of Telzir and the immunological response in this population are acceptable and unchanged compared to the previous available data.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation requested		**Type**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

Update of SmPC sections 4.8 and 5.1 with additional information on safety, antiviral response and treatment resistance in HIV-1 infected paediatric subjects, based on results of studies previously submitted as post-authorisation measures. In addition, the Product information is being updated to the latest QRD template version and editorial changes are implemented in SmPC sections 4.4, 4.8 and 5.1.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.