European Medicines Agency

London, 23 February 2009
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ASSESSMENT REPORT FOR TELZIR

International non-proprietary name:
fosamprenavir

Procedure No: EMEA/H/C/000534/II/0041

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

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I. RECOMMENDATION

This type II variation relates to the following changes: Update of section 4.2 "Posology and Method of Administration", 4.3 "Contraindications", 4.4 "Special warnings and precautions for use" and 5.2 "Pharmacokinetic properties" of the Summary of Product Characteristics (SPC) and section 2 "Before you take Telzir" and section 3 "How to take Telzir" of the Package Leaflet (PL) with data from clinical study APV10017 to implement dosing recommendation in patients with severe hepatic impairment.

Based on the review of the data on safety and efficacy, this type II variation application:

☒ **is approvable**. Since all issues **have been resolved**. The amendments to be introduced in the product information are acceptable.

II. ASSESSMENT

II.1. Introduction

A Marketing Authorisation was granted by the European Commission on 12 July 2004 for Telzir (fosamprenavir – FPV). FPV in combination with low dose ritonavir (RTV) is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults, adolescents and children of 6 years and above in combination with other antiretroviral (ARV) medicinal products. For ARV naïve and experienced adult patients the recommended dose is 700 mg FPV twice daily with 100 mg RTV twice daily, in combination with other antiretroviral medicinal products. FPV is rapidly and almost completely hydrolysed to amprenavir (APV) and inorganic phosphate prior to reaching the systemic circulation. The conversion of FPV to APV appears to primarily occur in the gut epithelium.

APV is primarily metabolised by the cytochrome P450 3A4 (CYP3A4) enzyme. RTV, also an HIV PI, is a CYP3A4 substrate and is a potent inhibitor of CYP3A4. RTV acts as a pharmacokinetic (PK) enhancer, resulting in an increased plasma APV concentration by inhibiting APV metabolism. APV is also a CYP3A4 inhibitor, and both APV and RTV may induce CYP3A4. Therefore medicinal products that are inducers, inhibitors or substrates of CYP3A4 must be used with caution when administered concurrently with FPV and RTV.

As no specific study was performed in patients with hepatic impairment with Telzir, the MAH was required to provide adequate data to support the use of Telzir in patients with various degrees (including severe) of hepatic impairment as a follow-up measure (FUM 014) to be fulfilled post-authorisation.

Part of this FUM was submitted in December 2006 in the format of a type II variation (II/20 approved on 2 July 2007) in order to update the SPC, subsequent to a phase I, parallel, open-label, two week, repeat-dose study (APV 10017) designed to evaluate the plasma APV and RTV pharmacokinetics in HIV-1 infected adult patients with mild, moderate, and severe hepatic impairment compared to matched control patients with normal hepatic function. At this time, results were only provided for patients with mild and moderate hepatic impairment but were not available for patients with severe hepatic impairment, as the recruitment was still ongoing for this group.

As a result of this type II variation, the following dosing recommendations were adopted for patients with mild and moderate hepatic impairment:

"For adults with mild hepatic impairment (Child-Pugh score: 5-6) the recommended dose is 700 mg fosamprenavir twice daily with 100 mg ritonavir once daily.
For adults with moderate hepatic impairment (Child-Pugh score: 7-9) the recommended dose is 450 mg fosamprenavir twice daily with 100 mg ritonavir once daily."

Since, at the time, no data were available for patients with severe hepatic impairment, FPV in combination with RTV remained contra-indicated in these patients.

Noteworthy, the number of HIV infected patients with underlying hepatic impairment receiving FPV/RTV, since the approval for use in mild/moderate hepatic impairment in the EU on 2 July 07, is unknown. However, ongoing observational cohorts study (WEUKSTV2430) being conducted in the EU will assess the post-marketing safety experience in this patient population, in line with a CHMP request.

Within this current submission, the MAH provides the remaining results of the previously submitted study APV 10017. These results only concern the population of patients with severe hepatic impairment with their matching control with normal hepatic function.

II.2 Clinical Aspects

The design of study APV 10017 was previously assessed in the setting of the type II variation II/20 approved in July 2007.

<table>
<tr><td>Title</td><td>A Phase I, Parallel, Open-label, Multicenter, Two Week, Repeat-dose Study Evaluating Plasma Amprenavir Pharmacokinetics in HIV-1-infected Adult Patients with Mild, Moderate or Severe Hepatic Impairment Receiving Fosamprenavir + Ritonavir Compared to Matched Control Patients with Normal Hepatic Function: Analyses of Mild and Moderate Hepatic Impairment.</td></tr>
<tr><td>Patients</td><td>Adult male and female HIV-1 infected patients from the US and EU, 18 to 65 years of age, with a body mass index (BMI) within the range of 19-35 kg/m^2
Patients were either hepatically impaired or had normal hepatic function.
The patients classified as hepatically impaired had liver fibrosis with known medical history of alcohol abuse. The degree of impairment was defined with Child-Pugh scores. Hepatically impaired patients could not have signs of hepatic function deterioration.
Patients must have had clinically stable HIV-1 disease for 3 months prior to study entry on current antiretroviral therapy (ART).
Concurrent ART consisting of NRTIs or N(t)RTIs was allowed during the study; concurrent use of NNRTIs and protease inhibitors (PIs) was not allowed.</td></tr>
<tr><td>Phase</td><td>1</td></tr>
<tr><td>Study Centres</td><td>Multicentre study (USA, Puerto Rico and Spain)</td></tr>
<tr><td>Study Period</td><td>16 November 2004 – 06 November 2007.
The severe cohort initiation date was 11 May 2006.</td></tr>
<tr><td>Design</td><td>Patients were enrolled into groups based on hepatic function status.
<table>
<tr><th>Group</th><th>N</th><th>Hepatic Function Status</th><th>Dosing Regimen</th></tr>
<tr><td>A</td><td>10</td><td>Mild Hepatic Impairment[1]</td><td>FPV 700mg BID + RTV 100mg QD</td></tr>
<tr><td>B</td><td>10</td><td>Moderate Hepatic Impairment[2]</td><td>FPV 300mg BID + RTV 100mg QD</td></tr>
<tr><td>C</td><td>10</td><td>Moderate Hepatic Impairment[2]</td><td>FPV 700mg QD + RTV 100mg QD</td></tr>
<tr><td>D[4]</td><td>10</td><td>Normal Hepatic Function</td><td>FPV 700mg BID + RTV 100mg BID</td></tr>
<tr><td>E[6]</td><td>10</td><td>Severe Hepatic Impairment[3]</td><td>FPV 300mg BID + RTV 100mg QD</td></tr>
<tr><td>F[5,6]</td><td>10</td><td>Normal Hepatic Function</td><td>FPV 700mg BID + RTV 100mg BID</td></tr>
</table>
1. As determined by Child-Pugh score of 5-6
2. As determined by Child-Pugh score of 7-9
3. As determined by Child-Pugh score of 10-15
4. Subjects in Group D were enrolled to match subjects in Group B based on sex, weight (± 5 kg), and age (± 5 years).
5. Subjects in Group F are being enrolled to match subjects in Group E based on sex, weight (± 5 kg) and age (± 5 years).
6. Enrollment into Groups E and F is ongoing.
This current report presents the data for patients with severe hepatic impairment (Group E) and their matched controls (Group F).</td></tr>
<tr><td>Number of</td><td>Planned: 10 patients by group (E and F) ; Enrolled: 11 patients in group E and 7</td></tr>
</table>

patients	patients in group F.
Objectives	Primary • To compare plasma APV PK in HIV-1 infected patients with severe hepatic impairment (as defined by Child-Pugh score of 10-15) receiving FPV 300mg BID with a reduced dosing frequency of RTV 100mg once daily to patients with normal hepatic function receiving FPV 700mg BID + RTV 100mg BID. Secondary • To compare plasma RTV PK in HIV-1 infected patients with severe hepatic impairment (as defined by Child-Pugh score of 10-15) receiving FPV 300mg BID + RTV 100mg once daily to patients with normal hepatic function receiving FPV 700mg BID + RTV 100mg BID. • To describe plasma FPV concentrations in HIV-1 infected patients with normal hepatic function and in patients with mild, moderate, and severe hepatic impairment following repeat doses of FPV + RTV. • To describe the percent APV protein binding in HIV-1 infected patients with normal hepatic function and in patients with mild, moderate, and severe hepatic impairment following repeat doses of FPV + RTV. • To assess the safety and tolerability of repeat doses of FPV + RTV in HIV-1 infected patients with mild, moderate, and severe hepatic impairment.
Endpoints	Primary Plasma APV Cmax, AUC(0-τ), and Cτ in HIV-1 infected patients with normal hepatic function or mild, moderate, severe hepatic impairment following repeat doses of FPV + RTV. Secondary • Albumin, bilirubin, ALT, AST, CHE (cholinesterase), ammonia, and PT (prothrombin time). • Plasma RTV Cmax, AUC(0-24), and Cτ, plasma FPV concentrations and plasma unbound APV concentrations (2 and 12-hour samples) in HIV-1 infected patients with normal or impaired hepatic function following repeat doses of FPV + RTV. • Plasma unbound APV concentrations (2 and 12-hour samples) in HIV-1 infected patients with normal hepatic function and in patients with mild, moderate, and severe hepatic impairment following repeat doses of FPV + RTV. • Adverse event (AE), concurrent medication/blood products, clinical laboratory, and vital signs assessments.
Criteria for evaluation	- Single pre-dose blood samplings were collected on the mornings of Days 3, 7, 10, 13 and 14. - Serial blood sampling were collected post-dose on Day 14 over 24 hours at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 hours. (24 hour sampling time for groups A, B and C) - Plasma total APV, FPV and RTV concentrations were assayed using validated LC/MS/MS method. The lower limit of quantification was 10 ng/ml for APV and RTV and 5 ng/ml for FPV. - Plasma unbound APV concentrations were measured at 2 hours (all patients), 12 hours (groups A, B, D) and 24 hours (group D) after dosing on Day 14. APV unbound concentration were measured in plasma ultrafiltrate with a validated LC/MS/MS method. The lower limit of quantification was 0.5 ng/ml. - Safety was assessed by adverse events (AEs), physical examination, clinical laboratory evaluations, electrocardiograms (ECGs), and vital signs. - In addition, Child-Pugh scores, plasma HIV-1 ribonucleic acid (RNA), CD4+ cell counts, Centers for Disease Control and Prevention (CDC) classification, and HIV-associated conditions were collected during the study.
Statistical methods	- The following plasma APV and RTV parameters were reported: AUCo-τ (over the dosing interval), Cavg the average plasma concentration over the dosing interval at steady-state (calculated as AUCo-τ/τ), CL/F the apparent oral clearance, the Cτ (average pre-dose concentrations collected at steady state), C2h unbound and Cτ

	unbound (plasma unbound APV concentration at 2 hours post-dosing and at the end of the dosing interval at steady-state), the percent unbound APV at 2 hours after dosing and at the end of the dosing interval, T1/2 the apparent terminal phase plasma half-life. - Descriptive statistics of plasma APV and RTV pharmacokinetic parameters (geometric means with 95% confidence intervals and coefficients of variation) were presented for each group. In addition the geometric least square (GLS) mean ratios and associated 90% confidence intervals (90% CI) were also presented.

Discussion on the Study design

In the previous assessment regarding study APV 10017 (Telzir II/20), the CHMP made the following comments:

This study is so far the unique study in hepatic impairment performed in the target population of HIV infected patients. This is one particular interest of this study to be underlined, even if it has implied to switch virologically stable patients to FPV/RTV at various tested adjusted doses that could have been suboptimal for these patients.
In addition,

- this study has enrolled patients with various degrees of hepatic impairment including the difficult-to-treat population of patients with severe hepatic impairment;
- this study was a multiple dose study therefore expected to give more confidence in the results for a medicinal product to be used chronically;
- the number of patients enrolled per arm is satisfactory;
- strictly in line with the European guideline, the unbound concentrations of medicinal product were measured. This is of relevant importance since unbound concentrations is very likely to be modified in patients with hepatic impairment (as a result of hypoproteinemia) for such a medicinal product highly protein bound;
- several dose adjustments were tested including two in patients with moderate hepatic impairment. In this field, it has to be underlined that a mix with fosamprenavir BID and ritonavir QD is not optimal since it might induce some confusion for patients. In addition the resort to the oral solution is also not optimal for patients Nevertheless it has to be admitted that given the unique 700 mg dosage the MAH does not have much latitude to adjust the dose.

Overall, this study initiated at the time the European guideline was released for consultation is strictly in line with the spirit of the guideline.

The results of study APV 10017 relative to patients with severe hepatic impairment and their matching control with normal hepatic function are reported below.

1. Study population

Disposition

Number of Subjects	Severe Hepatic Impairment (Group E)	Normal Hepatic Function (Group F)	Total
Number of subjects planned, N:	10	10	20
Number of subjects enrolled, N	11	7	18[3]
Number of subjects dosed, N:	10	7	17
Number of subjects completed as planned, n (%):	7 (70)	7 (100)	14 (82)
Number of subjects withdrawn (any reason), n (%):	3 (30)	0	3 (18)
Number of subjects withdrawn for SAE, n (%):	0	0	0
Number of subjects withdrawn for AE, n (%):	2 (20)	0	2 (12)
Reasons for subject withdrawal, n (%) Adverse events Protocol violation	 2 (20)[1] 1 (10)[2]	 0 0	 2 (12) 1 (6)

Severe hepatic impairment = hepatic fibrosis + Child-Pugh score of 10-15
Group E: FPV 300mg BID + RTV 100mg once daily x 14 days
Group F: FPV 700mg BID + RTV 100mg BID x 14 days
1. Subject 53 completed a single day of dosing whereas Subject 283 completed 13/14 days of dosing.
2. Subject 291 Completed the 14 day dosing period, missing a single dose of FPV on the evening of Day 12.
3. Subject 154 was randomized, but not dosed.

A total of 17 patients were enrolled in the study in Groups E and F and received study medications. Three patients in the severe hepatic impairment cohort withdrew from the study, two for adverse events and one due to a protocol violation.

Demographic and baseline characteristics

Demographic characteristics were generally similar between the two treatment groups.

Table 1 Summary of Demographic Characteristics in Apv10017 (Safety Population)

Demographics	Severe Hepatic Impairment (Group E) N=10	Normal Hepatic Function (Group F) N=7	Total N=17
Age in Years, Mean (Range)	42.8 (38, 53)	43.9 (33, 48)	43.2 (33, 53)
Sex, n (%) Female: Male:	 1 (10) 9 (90)	 1 (14) 6 (86)	 2 (12) 15 (88)
BMI, Mean (Range)	24.95 (20.4, 33.0)	26.59 (20.7, 31.6)	25.62 (20.4, 33.0)
Height, Mean (Range)	171.70 (160.0, 193.0)	168.71 (155.0, 179.0)	170.47 (155.0, 193.0)
Weight, Mean (Range)	73.41 (55.5, 100.7)	75.64 (62.0, 93.7)	74.33 (55.5, 100.7)
Ethnicity, n (%) Hispanic or Latino: Not Hispanic or Latino:	 5 (50) 5 (50)	 2 (29) 5 (71)	 7 (41) 10 (59)
Race, n (%) White – White/Caucasian/European Heritage	10 (100)	7 (100)	17 (100)

Severe hepatic impairment = hepatic fibrosis + Child-Pugh score of 10-15
Group E: FPV 300mg BID + RTV 100mg once daily x 14 days
Group F: FPV 700mg BID + RTV 100mg BID x 14 days

Table 2 Summary of Baseline Characteristics in APV10017 (SafetyPopulation)

Baseline Characteristic	Severe Hepatic Impairment (Group E) N=10	Normal Hepatic Function (Group F) N=7	Total N=17
Baseline Plasma HIV-1 RNA, n (%)			
<50 copies/mL	6 (60)	6 (86)	12 (71)
>50 copies/mL	4 (40)	1 (14)	5 (29)
Baseline CD4+ cell count (cells/mm^3)			
n	9	7	
Mean (SD)	264 (101)	746 (712)	N/A
Median	260	470	
(Range)	(90, 420)	(90, 1280)	
HIV Risk Factors, n (%)			
Injectable drug use	7 (70)	0	7 (41)
Homosexual contact	1 (10)	5 (71)	6 (35)
Heterosexual contact	1 (10)	2 (29)	3 (18)
Transfusion	0	0	0
Hemophilia-associated injections	0	0	0
CDC Classification, n (%)			
A: Asymptomatic or lymphadenopathy or acute HIV	7 (70)	4 (57)	11 (65)
B: Symptomatic, not AIDS	0	1 (14)	1 (6)
C: AIDS	3 (30)	2 (29)	5 (29)
Hepatitis B and C Serology, n (%)			
Hepatitis B Surface Antigen			
Non-reactive	9 (90)	7 (100)	16 (94)
Reactive	1 (10)	0	1 (6)
Hepatitis C Antibody			
Non-reactive	2 (20)	7 (100)	9 (53)
Reactive	3 (30)	0	3 (18)
Repeatedly Positive	5 (50)	0	5 (29)

Severe hepatic impairment = hepatic fibrosis + Child-Pugh score of 10-15
Group E: FPV 300mg BID + RTV 100mg once daily x 14 days
Group F: FPV 700mg BID + RTV 100mg BID x 14 days

Patients in the severe hepatic impairment had lower CD4+ cell counts and were more likely to be co-infected with Hepatitis C when compared with patients having normal hepatic function. Risk factors also differed between groups, with injectable medicinal product use being the most common risk factor (7/10, 70%) for patients with severe hepatic impairment compared with homosexual contact being the most common risk factor (5/7, 71%) for patients with normal hepatic function.

Child-Pugh scores

At Pre-baseline (Day -4), patients in the severe hepatic impairment group had total Child-Pugh scores ranging from 10 to 13. Most hepatically impaired patients had Grade 1 encephalopathy (8/10, 80%). Most patients had mild (Grade 2; 4/10, 40%) or moderate (Grade 3, 5/10, 50%) ascites.

2. Pharmacokinetic results

Amprenavir concentrations

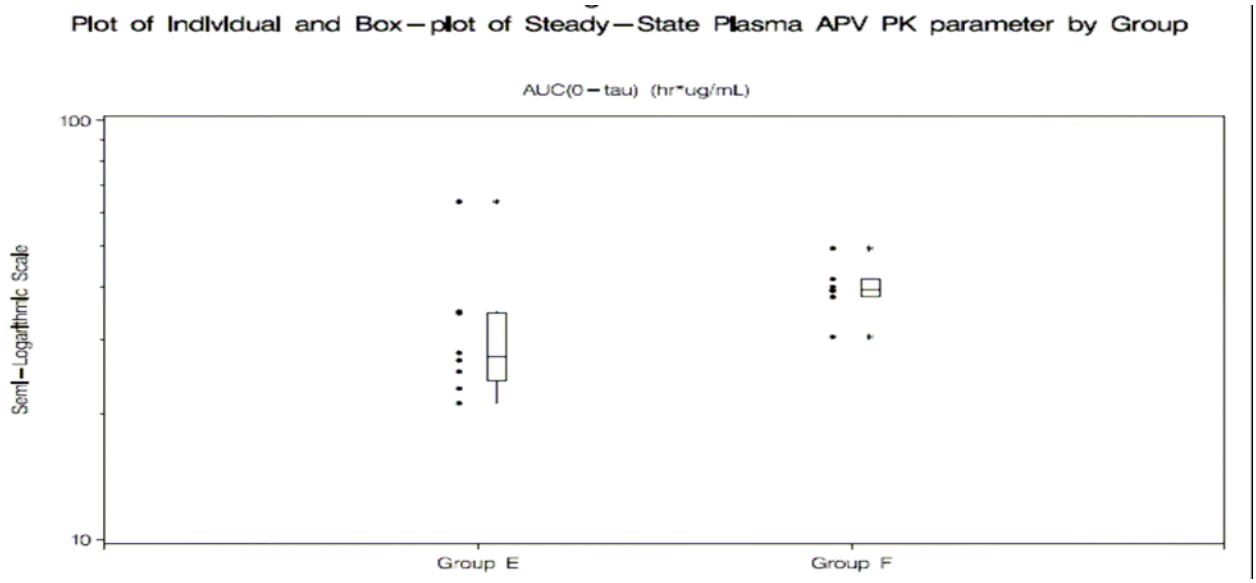
Table 3 Summary and Statistical Comparisons of Selected Plasma APV Pharmacokinetic Parameters for Severe Hepatic Impairment and Normal Hepatic Function Groups in APV10017

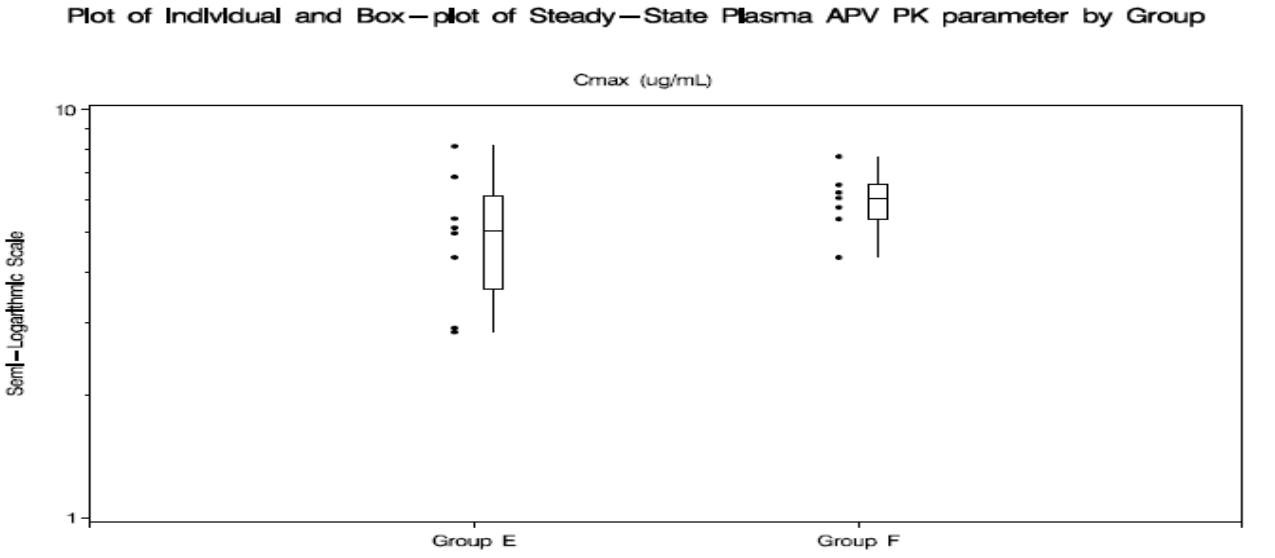
Plasma APV PK Parameter	Geometric Mean (95% CI) [CVb%]		GLS Mean Ratio (90% CI)
	Severe Hepatic Impairment (Group E) N=8[1]	Normal Hepatic Function (Group F) N=7[2]	Severe Hepatic Impairment vs Normal Hepatic Function
Dose-Normalized			
DN-AUC(0-τ) (µg.h/mL)	70.8 (52.8, 94.9) [36]	39.4 (34.5, 45.0) [14]	1.80 (1.40, 2.31)
DN-Cmax (µg/mL)	11.2 (8.22, 15.3) [38]	5.94 (5.05, 6.99) [18]	1.88 (1.44, 2.47)
DN-Cτ (µg/mL)	3.17 (1.99, 5.05) [60]	2.19 (1.82, 2.64) [20]	1.45 (0.97, 2.15)
Observed			
AUC(0-τ) (µg.h/mL)	30.3 (22.6, 40.7) [36]	39.4 (34.5, 45.0) [14]	0.77 (0.60, 0.99)
Cmax (µg/mL)	4.80 (3.52, 6.54) [38]	5.94 (5.05, 6.99) [18]	0.81 (0.62, 1.06)
Cτ (µg/mL)	1.36 (0.85, 2.16) [60]	2.19 (1.82, 2.64) [20]	0.62 (0.42, 0.92)
CL/F (mL/min)	141 (105, 189) [36]	254 (222, 290) [14]	0.56 (0.43, 0.72)
t1/2 (h)	6.13 (4.31, 8.72) [40]	5.62 (3.84, 8.23) [38]	1.09 (0.75, 1.58)

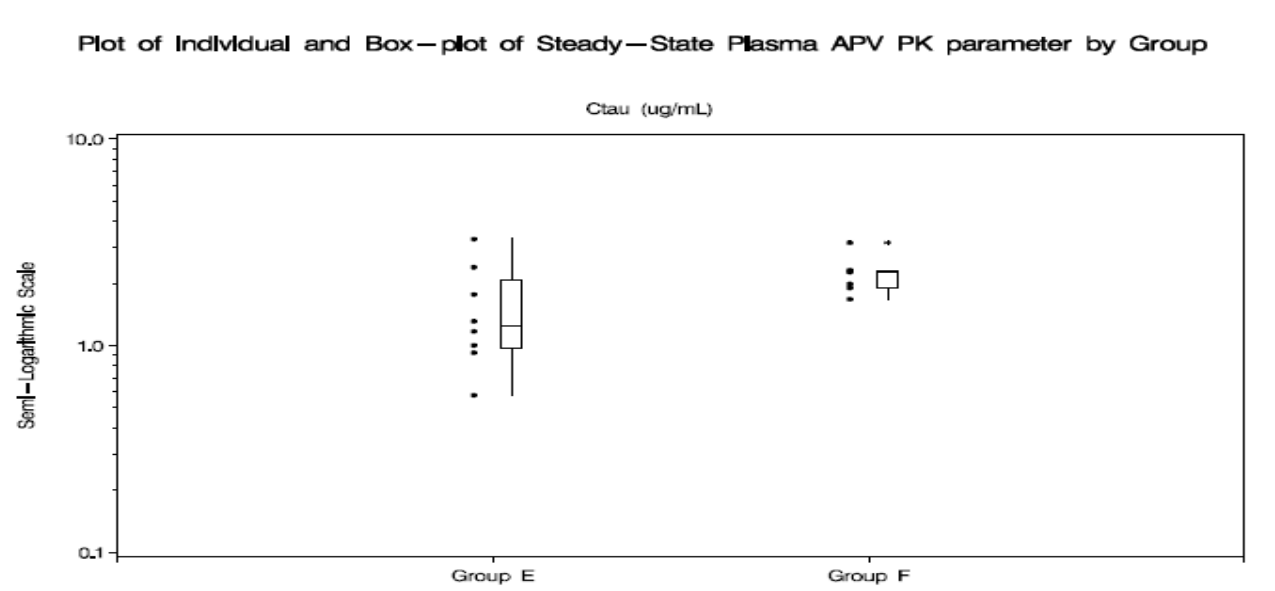
Severe hepatic impairment = hepatic fibrosis + Child-Pugh score of 10-15
Group E: FPV 300mg BID + RTV 100mg once daily x 14 days
Group F: FPV 700mg BID + RTV 100mg BID x 14 days
DN=dose normalized to FPV 700mg
1. N=7 for t1/2
2. N=6 for t1/2

When plasma APV PK was normalised to a 700mg FPV dose, severe hepatic impairment significantly increased plasma total APV Dose Normalised (DN)-AUC(0-τ) by 80%, DN-C_{max} by 88%, and DN-Cτ by 45% following administration of FPV/RTV. The dosage regimen tested in severe hepatic impairment, FPV 300mg BID + RTV 100mg once daily, delivered 23% lower plasma APV $AUC_{(0-\tau)}$, 19% lower Cmax, and 38% lower Cτ values compared to patients with normal hepatic function receiving FPV/RTV 700/100mg BID. Plasma Median t_{max} was delayed 1.5 hours in the severe hepatic impairment group and APV $t_{1/2}$ values were similar between patients with severe hepatic impairment and patients with normal hepatic function. Variability in plasma APV PK values was higher for the severe hepatic impairment group.

Plots for individual APV PK parameters are reported below.







Unbound Amprenavir concentrations

Table 4 Summary and Statistical Comparisons of Plasma Unbound APV Concentrations for Severe Hepatic Impairment and Normal Hepatic Function Groups in APV10017

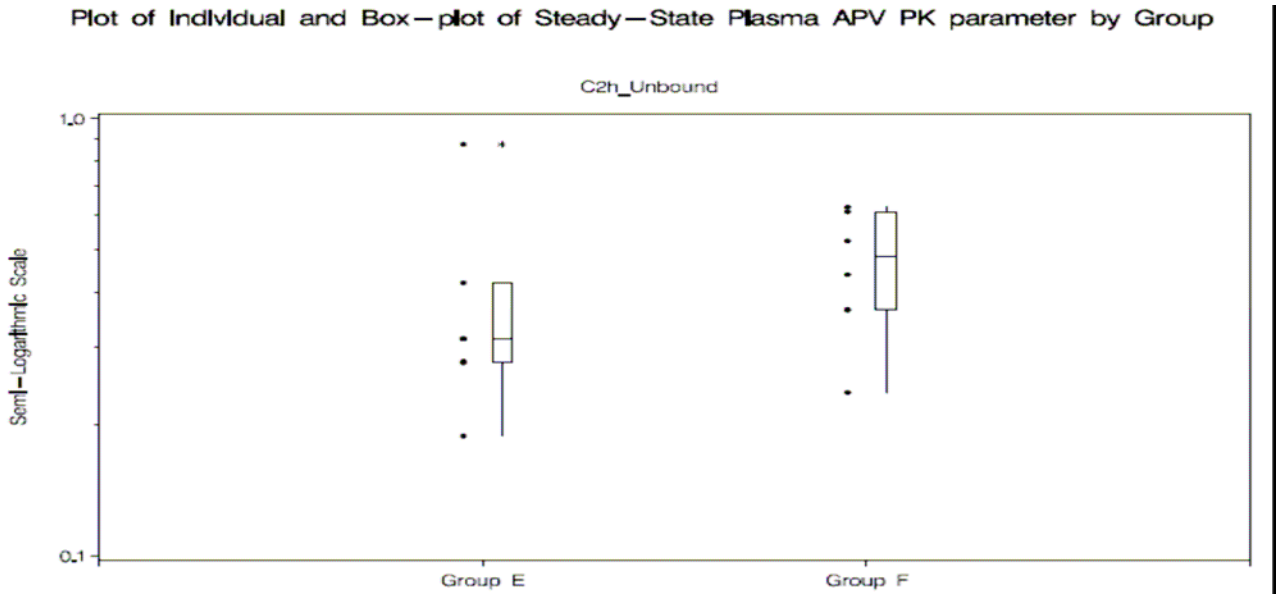
Plasma Unbound APV Parameter	Geometric Mean (95% CI) [CVb%]		GLS Mean Ratio (90% CI)
	Severe Hepatic Impairment (Group E) N=8[1]	Normal Hepatic Function (Group F) N=6[2]	Severe Hepatic Impairment vs Normal Hepatic Function
2-h concentration (μg/mL)	0.34 (0.22, 0.53) [51]	0.44 (0.30, 0.65) [38]	0.77 (0.50, 1.18)
Cτ (μg/mL)	0.12 (0.05, 0.26) [122]	0.12 (0.07, 0.20) [43]	0.96 (0.42, 2.17)
2-h % unbound	8.37 (6.57, 10.7) [27]	8.97 (5.14, 15.7) [57]	0.93 (0.62, 1.40)
Cτ % unbound	9.37 (6.24, 14.1) [52]	5.69 (3.72, 8.69) [35]	1.65 (1.05, 2.58)

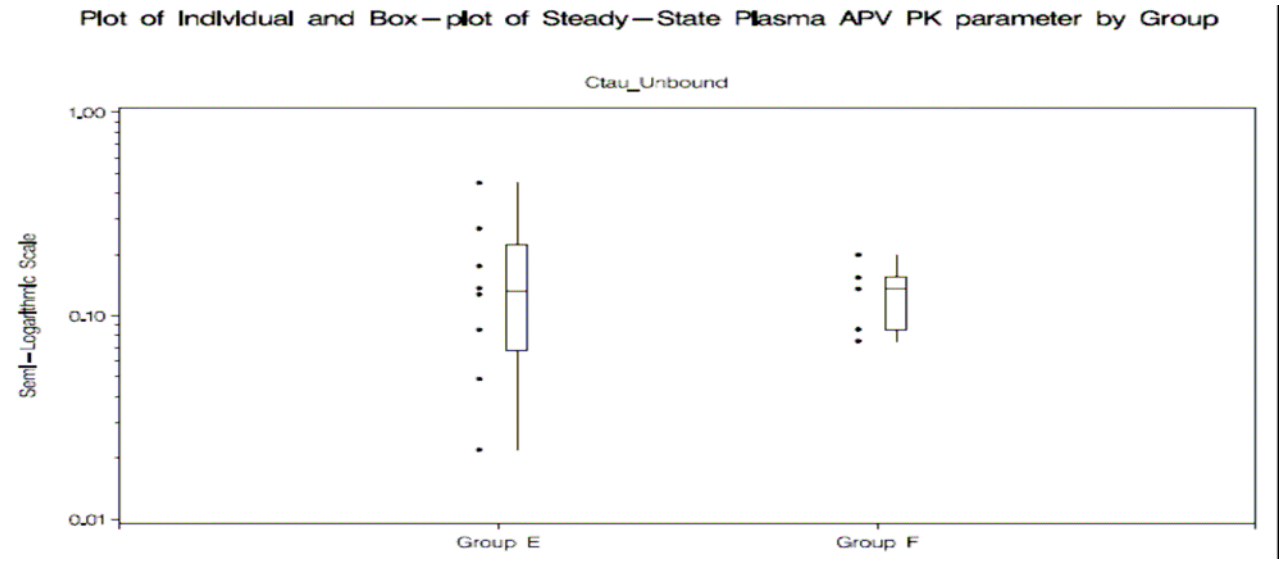
Severe hepatic impairment = hepatic fibrosis + Child-Pugh score of 10-15
Group E: FPV 300mg BID + RTV 100mg once daily x 14 days
Group F: FPV 700mg BID + RTV 100mg BID x 14 days
1. N=7 for 2-hour assessments
2. N=5 for Cτ assessments

Patients with severe hepatic impairment had a higher %unbound APV 12 hours after dosing and similar plasma unbound concentration at 12 hours after dosing (unbound Cτ) compared to patients with normal hepatic function. However, at the 2-hour time point, there was no clear difference in the %unbound APV between the groups, and patients with severe hepatic impairment receiving FPV 300mg BID + RTV 100mg once daily had lower plasma unbound APV concentration 2 hours after dosing (C2h) than patients with normal hepatic function receiving FPV/RTV 700/100mg BID.

On average, plasma unbound APV Cτ values (the parameter considered to be associated with virologic efficacy) were comparable in patients with severe hepatic impairment and in patients with normal hepatic function.

Plots for individual unbound APV PK parameters are reported below.





Discussion on the PK results

The APV PK parameters were lower (about -20 to -30%) in patients with severe hepatic impairment receiving FPV 300 mg BID + RTV 100 mg QD compared to patients with normal hepatic function receiving FPV/RTV 700/100 mg BID. The PK variability was also increased in patients with severe hepatic impairment.

Of importance, the mean Cτ concentration of unbound APV is similar in patients with severe hepatic impairment compared with patients with normal hepatic function, whereas the mean C2h concentration of unbound APV is decreased by more than 20% in patients with severe hepatic impairment compared with patients with normal hepatic function.

For both parameters it should be noted that the PK variability is increased in patients with severe hepatic impairment compared with patients with normal hepatic function and therefore the bounds for confidence interval are very large.

Ritonavir concentrations

Table 5 Summary and Statistical Comparisons of Selected Plasma RTV Pharmacokinetic Parameters for Severe Hepatic Impairment and Normal Hepatic Function Groups in APV10017

Plasma RTV PK Parameter	Geometric Mean [95% CI] (CVb%)		GLS Mean Ratio [90% CI]
	Severe Hepatic Impairment (Group E) N=8	Normal Hepatic Function (Group F) N=7	Severe Hepatic Impairment vs Normal Hepatic Function
AUC(0-τ)[1] (µg.h/mL)	10.8 (5.72, 20.5) [89]	3.88 (2.37, 6.34) [57]	2.80 (1.52, 5.16)
Cavg[2] (µg/mL)	0.45 (0.24, 0.86) [89]	0.32 (0.20, 0.53) [57]	1.40 (0.76, 2.58)
Cmax (µg/mL)	1.26 (0.57, 2.78) [121]	0.77 (0.38, 1.56) [90]	1.64 (0.74, 3.64)
Cτ (µg/mL)	0.23 (0.15, 0.35) [53]	0.17 (0.12, 0.24) [41]	1.38 (0.91, 2.09)
CL/F (mL/min)	154 (81.1, 291) [89]	430 (263, 703) [57]	0.36 (0.19, 0.66)
t1/2 (h)	8.88 (6.91, 11.4) [28]	5.05 (3.29, 7.76) [49]	1.76 (1.22, 2.53)

Severe hepatic impairment = hepatic fibrosis + Child-Pugh score of 10-15
Group E: FPV 300mg BID + RTV 100mg once daily x 14 days
Group F: FPV 700mg BID + RTV 100mg BID x 14 days

1. RTV AUC(0-τ) is over 24 hour dosing interval for severe HI group and over 12 hour dosing interval for normal hepatic function group. Comparison of AUC(0-τ) between the groups shows the impact of severe HI on plasma RTV exposure.
2. Cavg normalizes AUC for the dosing interval; i.e., Cavg = AUC(0-τ)/24 for severe HI group and Cavg = AUC(0-τ)/12 for normal hepatic function group. Comparison of Cavg between the groups allows a comparison of observed RTV exposures over the same interval of time.

Despite reducing the RTV dose to 100mg once daily, patients with severe hepatic impairment had 64% higher plasma RTV C_{max}, 40% higher Cavg, and 38% higher Cτ values compared to patients with normal hepatic function receiving FPV/RTV 700/100mg BID.
The variability in RTV PK parameters was increased in patients with severe hepatic impairment compared with patients with normal hepatic function.

Discussion on the Ritonavir concentrations

The exposure of RTV is highly increased in patients with severe hepatic impairment (AUC multiplied by almost a 3 fold factor) compared to patients with normal hepatic function. This increase in RTV exposure could lead to a deterioration of its safety profile.

3. Safety results

A total of 9 of 17 patients (53%) experienced one or more treatment-emergent adverse event (AE) irrespective of cause during the study. Gastrointestinal disorders was the system organ class with the most AEs reported (Group E: 4/10 (40%); Group F: 0).

A total of 3 of 17 patients (18%) reported one or more treatment-emergent drug-related AE during the study. All drug-related AEs were reported by patients in the severe hepatic impairment group. Dyspepsia was the only drug-related AE reported by more than one subject.

Two patients, both in the severe hepatic impairment group were withdrawn from the study and discontinued from investigational product due to AEs. Subject 53 (Group E) discontinued from investigational product following the first day of dosing due to Grade 1 vomiting that the investigator considered to be related to study medicinal product. Subject 283 (Group E) was withdrawn from the study due to Grade 4, serious, hepatic encephalopathy that the investigator considered not to be related to study medications.

There was no meaningful change in clinical laboratory evaluations.

The MAH acknowledged that APV10017 was a short term PK study, and that the long-term safety of the combination in patients with severe hepatic impairment is unknown. MAH proposed to study the safety of FPV/RTV-based combination antiretroviral therapy (cART) in this population in the ongoing cohort study WEUKSTV2430, an observational study involving EU cohorts (ICONA, HEPAVIH, MASTER) which is currently assessing the long-term safety of the approved FPV/RTV dosing regimen in patients with mild and moderate hepatic impairment. The MAH proposed to address the safety of this regimen over the longer term in patients with severe hepatic impairment in its ongoing observational cohort Study WEUKSTV2430 (FUM 45 and FUM 45.1; letter of undertaking dated 30 April 2007).

Discussion on the safety results

No safety concern emerged in patients with severe hepatic impairment in this study. However, as underlined by the MAH, the number of patients is very limited. Therefore, the MAH's proposal to investigate the safety of FPV/RTV treatment regimen in patients with severe hepatic impairment in the ongoing cohort study is fully endorsed.

4. Pharmacodynamic results

All of the patients who entered the study with plasma HIV-1 RNA <50 copies/ml remained suppressed through Day 14. Additionally, all of the patients entering the study with plasma HIV-1 RNA >50 copies/ml had a decrease in their plasma HIV-1 RNA levels between Baseline and Day 14, with one subject in each treatment group achieving undetectable (<50 copies/mL) levels on Day 14. No substantial changes in CD4+ cell counts occurred in either treatment group from Baseline to Day 14.

III. CHANGES TO THE PRODUCT INFORMATION

Of note, the same changes are proposed for Telzir film-coated tablets and for Telzir 50 mg/ml oral solution. They are reported below.

CHMP's comments and proposed changes (addition, ~~deletion~~) are reported below.

Summary of Product Characteristics

4.2 Posology and method of administration

...

Hepatic impairment

For adults with mild hepatic impairment (Child-Pugh score: 5-6) the recommended dose is 700 mg fosamprenavir twice daily with 100 mg ritonavir once daily.

For adults with moderate hepatic impairment (Child-Pugh score: 7-9) the recommended dose is 450 mg fosamprenavir twice daily with 100 mg ritonavir once daily. As it is not possible to achieve this fosamprenavir dose using the tablet formulation, these patients should be treated with fosamprenavir oral suspension.

For adults with severe hepatic impairment (Child-Pugh score: 10-15): fosamprenavir should be used with caution and at a reduced dose of 300 mg fosamprenavir twice daily with 100 mg ritonavir once daily. As it is not possible to achieve this fosamprenavir dose using the tablet formulation, these patients should be treated with fosamprenavir oral suspension.

CHMP's comment:
The MAH's proposal to specify that Telzir should be used **with caution** in adults with severe hepatic impairment is supported, given the characteristics of this difficult-to-treat population more at risk of adverse events and in view of the PK results (high inter-variability, increase in RTV exposure).
To avoid administration error of ritonavir, it is worth emphasising on the once daily regimen as in the package leaflet:" **only"** once daily for all the wording of the recommendation in case of hepatic impairment (i.e. mild, moderate, severe)

Even with these dose adjustments for adults with mild ~~or~~, moderate or severe hepatic impairment, some patients may have higher than anticipated amprenavir and ritonavir plasma concentrations due to inter-patient variability (see section 5.2), therefore safety monitoring is warranted.

CHMP's comment:
Due to the high variability lower or higher exposure can be observed therefore the recommendation should be completed as follows:

"Even with these dose adjustments for adults ~~with mild, moderate or severe hepatic impairment~~, some patients with hepatic impairment may have higher or lower ~~than anticipated~~ amprenavir and/or ritonavir plasma concentrations as compared to patients with normal hepatic function due to increased inter-patient variability (see section 5.2), therefore ~~safety~~ a close monitoring of safety and virologic response is warranted.

~~Telzir in combination with ritonavir is contraindicated in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).~~

CHMP's comment:
For completeness, the MAH should propose a statement about the lack of data for children with hepatic impairment, along with a recommendation for the prescriber.

4.3 Contraindications

...

~~Patients with severe hepatic impairment (see sections 4.4 and 5.2).~~

...

4.4 Special warnings and precautions for use

…

Liver disease

Telzir with ritonavir should be used with caution and at reduced doses in adults with mild ~~or~~, moderate or severe hepatic impairment (see section 4.2) ~~and is contraindicated in patients with severe hepatic impairment (see section 4.3).~~ .

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products.

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

5.2 Pharmacokinetic properties

Hepatic impairment

…

The plasma amprenavir pharmacokinetics were evaluated in a 14 day repeat-dose study in HIV-1 infected adult subjects with mild ~~or~~, moderate or severe hepatic impairment receiving fosamprenavir with ritonavir compared to matched control subjects with normal hepatic function.

…

In subjects with moderate hepatic impairment (Child-Pugh score of 7-9), a reduced dose of fosamprenavir 450 mg twice daily with a reduced dosing frequency of ritonavir 100 mg once daily is predicted to deliver similar plasma amprenavir C_{max} and AUC(0-12), but approximately 35 % lower plasma total amprenavir C12 values and approximately 88 % higher plasma unbound amprenavir C12 values than achieved in subjects with normal hepatic function receiving the standard fosamprenavir with ritonavir 700 mg / 100 mg twice daily regimen.

In subjects with severe hepatic impairment (Child-Pugh score of 10-13), a reduced dose of fosamprenavir 300 mg twice daily with a reduced dosing frequency of ritonavir 100 mg once daily delivered 19% lower plasma amprenavir Cmax, 23% lower AUC(0-12), and 38% lower C12 values, but similar unbound plasma amprenavir C12 values than achieved in subjects with normal hepatic function receiving the standard fosamprenavir with ritonavir 700 mg / 100 mg twice daily regimen. Despite reducing the dosing frequency of ritonavir, subjects with severe hepatic impairment had 64% higher ritonavir C_{max}, 40% higher ritonavir Cavg, and 38% higher ritonavir C12 than achieved in subjects with normal hepatic function receiving the standard fosamprenavir with ritonavir 700 mg / 100 mg twice daily regimen.

CHMP's comment:
It is considered more appropriate to mention in the SPC the value of AUC instead of Cavg for ritonavir. Since AUC was increased by about 3 fold, it is worth giving this information to prescribers. Therefore, the following modification is proposed:

"In patients with severe hepatic impairment (Child-Pugh score of 10-13), a reduced dose of fosamprenavir 300 mg twice daily with a reduced dosing frequency of ritonavir 100 mg once daily

delivered 19% lower plasma amprenavir C_{max}, 23% lower AUC(0-12), and 38% lower C12 values, but similar unbound plasma amprenavir C12 values than achieved in patients with normal hepatic function receiving the standard fosamprenavir with ritonavir 700 mg / 100 mg twice daily regimen. Despite reducing the dosing frequency of ritonavir, patients with severe hepatic impairment had 64% higher ritonavir C_{max}, ~~40% higher ritonavir Cavg~~ 2.8 fold higher AUC, and 38% higher ritonavir C12 than achieved in patients with normal hepatic function receiving the standard fosamprenavir with ritonavir 700 mg / 100 mg twice daily regimen."

Fosamprenavir with ritonavir was generally well-tolerated in subjects with mild ~~to,~~ moderate or severe hepatic impairment, and these regimens had similar adverse event and clinical laboratory profiles as previous studies of HIV-1 infected subjects with normal hepatic function.

~~Fosamprenavir with ritonavir is contraindicated in patients with severe hepatic impairment (see section 4.3).~~

Package Leaflet

2. BEFORE YOU TAKE TELZIR

...

Don't take Telzir:

...

~~□ **if you have severe liver disease** (see the next section 'Take special care with Telzir').~~

...

3. HOW TO TAKE TELZIR

...

Adults with liver disease

If you have mild liver disease, the dose is **one Telzir tablet (700 mg) twice daily** with 100 mg ritonavir **only once daily.** If you have moderate liver disease the recommended dose of Telzir is **450 mg twice daily** (using 9 ml of the oral suspension) with 100 mg ritonavir **only once daily**. If you have severe liver disease the recommended dose of Telzir is **300 mg twice daily** (using 6 ml of the oral suspension) with 100 mg ritonavir **only once daily.**

CHMP's comment:
It is proposed to adopt different statements for the Telzir tablet PL and for the Telzir oral solution PL, as follows:

Tablet

Adults with liver disease

If you have mild liver disease, the dose is **one Telzir tablet (700 mg) twice daily** with 100 mg ritonavir **only once daily.** If you have moderate or severe liver disease the recommended dose of Telzir has to be lowered (use Telzir oral suspension). ~~is **450 mg twice daily** (use Telzir oral suspension) with 100 mg ritonavir **only once daily**.~~

Oral suspension)

Adults with liver disease

If you have mild liver disease, the dose is **14 ml Telzir oral suspension** (700 mg fosamprenavir) **twice daily** with 100 mg ritonavir **only once daily.**
If you have moderate liver disease the dose is **9 ml Telzir oral suspension** (450 mg fosamprenavir) **twice daily** with 100 mg ritonavir **only once daily**.
If you have severe liver disease the dose is **6 ml Telzir oral suspension** (300 mg fosamprenavir) **twice daily** with 100 mg ritonavir **only once daily**.

IV. REQUEST FOR SUPPLEMENTARY INFORMATION

Based on the review of the data on clinical pharmacology, efficacy and safety within this procedure, this type II variation **could be approvable** provided that the CHMP's proposed changes for the SPC are taken into account.

Changes to the Product Information
The MAH should submit a revised Product Information considering the above comments and the changes requested in the SPC as detailed in part III of this Assessment Report.

The CHMP proposed to extend the timetable as follows:

☒ **30 days (including 15 days for Rapporteur assessment)**

V. ASSESSMENT OF THE RESPONSES TO THE REQUEST FOR SUPPLEMENTARY INFORMATION

Overall the MAH agreed on all the changes to the SPC and PL requested by CHMP or provided alternative wording with supporting rational that was considered satisfactory. Wording details are given below. No further changes are deemed necessary in the framework of this procedure.

Question 1:

SPC – Section 4.2 Posology and method of administration

- The MAH's proposal to specify that Telzir should be used with caution in adults with severe hepatic impairment is supported, given the characteristics of this difficult-to treat population more at risk of adverse events and in view of the PK results (high inter-variability, increase in RTV exposure).
  To avoid administration error of ritonavir, it is worth emphasizing on the once daily regimen as in the package leaflet: **"only"** once daily for all the wording of the recommendation in case of hepatic impairment (i.e. mild, moderate, severe).

The MAH considered that the wording "only once daily" is appropriate for the package leaflet, but that the SPC already clearly informs the prescribers that the dosage regimen for ritonavir is once daily. However, to provide further emphasis, the MAH proposed that the word "once" should be changed to bold type in the SPC. This proposal is endorsed by the CHMP.

- Due to the high variability lower or higher exposure can be observed therefore the recommendation should be completed as follows:
  "*Even with these dose adjustments for adults ~~with mild, moderate or severe hepatic impairment~~, some patients with hepatic impairment may have higher or lower ~~than anticipated~~ amprenavir and/or ritonavir plasma concentrations as compared to patients with normal hepatic function due to increased inter-patient variability (see section 5.2), therefore ~~safety~~ a close monitoring of safety and virologic response is warranted*."

The MAH agreed with this proposed wording in section 4.2 of the SPC. The CHMP has no further comment.

- For completeness, the MAH should propose a statement about the lack of data for children with hepatic impairment, along with a recommendation for the prescribers.

The following wording proposed by the MAH is endorsed by the CHMP: "No dose recommendation can be made for children and adolescents with hepatic impairment as no studies have been conducted in these age groups".

Question 2:

SPC – Section 5.2 Pharmacokinetic properties

…

Hepatic impairment

It is considered more appropriate to mention in the SPC the value of AUC instead of this of Cavg for ritonavir. Indeed, since AUC was increased by about 3 fold, it is worth giving this information to prescribers.

Expression of RTV exposure in section 5.2

RTV was administered BID to patients with normal hepatic function and QD to patients with severe hepatic impairment. The 2.8-fold increase in plasma RTV $AUC_{(0-\tau)}$, therefore, reflects exposures over different time intervals, specifically $AUC_{(0-12)}$ for the BID regimen and $AUC_{(0-24)}$ for the QD regimen. To represent exposure over the same interval of time either Cavg (calculated as $AUC_{(0-\tau)}/\tau$ for both the BID and QD regimens) or $AUC_{(0-24)}$ (where $AUC_{(0-\tau)}$ for the BID regimen (τ=12) is multiplied by 2 and the $AUC_{(0-\tau)}$ for the QD regimen (τ=24) is unchanged) can be used. In Section 5.2 of the SPC, the MAH emphasised the comparison of the observed plasma RTV AUC adjusted for the dosing interval difference because this is representative of the exposure that patients will have to RTV over a given period of time. This was the basis for the original proposal to include the comparison of RTV Cavg within Section 5.2 of the SPC.

The MAH accepted, however, to present AUC values in the SPC but proposed to represent RTV exposure as $AUC_{(0-24)}$ rather than $AUC_{(0-\tau)}$ for both regimens. In essence, patients with severe hepatic impairment receiving FPV 300mg BID + RTV 100mg QD will have 40% higher AUC's over a 24-hour period of time ($AUC_{(0-24)}$) than will patients with normal hepatic impairment receiving FPV/RTV 700/100mg BID.

This approach together with the following wording proposed by the MAH was endorsed by the CHMP:

"In subjects with severe hepatic impairment (Child-Pugh score of 10-13), a reduced dose of fosamprenavir 300 mg twice daily with a reduced dosing frequency of ritonavir 100 mg once daily delivered 19% lower plasma amprenavir C_{max}, 23% lower $AUC_{(0-12)}$, and 38% lower C12 values, but similar unbound plasma amprenavir C12 values than achieved in subjects with normal hepatic function receiving the standard fosamprenavir with ritonavir 700 mg / 100 mg twice daily regimen. Despite reducing the dosing frequency of ritonavir, subjects with severe hepatic impairment had 64% higher ritonavir C_{max}, 40% higher ritonavir ~~Cavg~~ $AUC_{(0-24)}$, and 38% higher ritonavir C12 than achieved in subjects with normal hepatic function receiving the standard fosamprenavir with ritonavir 700 mg / 100 mg twice daily regimen".

Question 3:

PL - Section 3 How to take Telzir

The CHMP proposed to adopt different statements for the Telzir tablet PL and for the Telzir oral solution PL as follows.

Tablet

Adults with liver disease

If you have mild liver disease, the dose is **one Telzir tablet (700 mg) twice daily** with 100 mg ritonavir **only once daily.** If you have moderate or severe liver disease the recommended dose of Telzir has to be lowered (use Telzir oral suspension). ~~is **450 mg twice daily** (use Telzir oral suspension) with 100 mg ritonavir **only once daily**~~.

Oral suspension

Adults with liver disease

If you have mild liver disease, the dose is **14 ml Telzir oral suspension** (700 mg fosamprenavir) **twice daily** with 100 mg ritonavir **only once daily.**

If you have moderate liver disease the dose is **9 ml Telzir oral suspension** (450 mg fosamprenavir) **twice daily** with 100 mg ritonavir **only once daily.**
If you have severe liver disease the dose is **6 ml Telzir oral suspension** (300 mg fosamprenavir) **twice daily** with 100 mg ritonavir **only once daily.**

The MAH accepted that the wording should be modified, but proposed for the tablets a more patient-friendly alternative wording, as follows, that is endorsed by the CHMP.
"If you have moderate or severe liver disease, the dose of Telzir has to be lowered. This dose adjustment can not be made with Telzir tablets. You must take Telzir oral suspension."

With regards to the proposal to amend the oral suspension PL, the MAH accepted the wording proposed by the CHMP. The CHMP has no further comment.

VI. OVERALL DISCUSSION AND BENEFIT-RISK ASSESSMENT

In the context of a public health need for ARV products to treat patients with severe hepatic impairment, the CHMP would like to emphasise the importance of study APV10017, especially that this study was well designed, in line with the European guideline.

Based on the pharmacokinetic results obtained in patients with severe hepatic impairment it is acceptable to recommend the dose studied in APV10017 for these patients i.e. FPV 300 mg twice daily with RTV 100 mg once daily.

At last, it is appreciated that the MAH proposes to study the safety of FPV/RTV in patients with severe hepatic impairment in the ongoing cohort study which is currently assessing the long-term safety of the approved FPV/RTV dosing regimen in patients with mild and moderate hepatic impairment.

The MAH's initial proposed change to the product information was appropriate. Indeed, the need for a close monitoring of patients, linked to the high inter-patient variability, was clearly mentioned. However the CHMP requested additional changes to the SPC and PL in order to further simplify the product information and to further clarify the recommendations to the treating physicians. The MAH addressed satisfactorily all requests made by the CHMP and provided the corresponding updated product information.

VII. EPAR CHANGES

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope:
Update of section 4.2 "Posology and Method of Administration", 4.3 "Contraindications", 4.4 "Special warnings and precautions for use" and 5.2 "Pharmacokinetic properties" of the Summary of Product Characteristics (SPC) and section 2 "Before you take Telzir" and section 3 "How to take Telzir" of the Package Leaflet (PL) with data from clinical study APV10017 to implement dosing recommendation in patients with severe hepatic impairment.

Scientific discussion:
Please note that this assessment report will be published after deletion of commercially confidential information.