18 July 2011

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Aptivus

tipranavir

Procedure No.: EMEA/H/C/000631/II/0049/G

Note

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

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19 May 2011
EMA/567400/2011
Human Medicines Development and Evaluation

CHMP variation assessment report

Type II variation EMEA/H/C/000631/II/0049/G

Name:	Aptivus
Common name:	tipranavir
Indication summary (as last approved):	treatment of HIV-1 infection
Marketing authorisation holder:	Boehringer Ingelheim International GmbH

1. Scientific discussion

1.1. Introduction

Aptivus (tipranavir - TPV) is a Human Immunodeficiency Virus type 1 (HIV-1) protease inhibitor (PI), indicated in co-administration with low dose ritonavir (RTV, if used as booster =/r) for combination antiretroviral (ARV) treatment of HIV infection in highly pre-treated patients with virus resistant to multiple PIs. Tipranavir must always be given with low dose RTV as a pharmacokinetic enhancer, and should only be used as part of an active combination ARV regimen in patients with no other therapeutic option. Tipranavir is available as capsule and oral solution. Tipranavir 250 mg capsule co-administered with low dose RTV, is indicated for combination ARV treatment of HIV-1 infection in highly pre-treated adults and adolescents 12 years of age or older with virus resistant to multiple PIs. Tipranavir 100 mg/ml oral solution, co-administered with low dose RTV, is indicated for combination ARV treatment of HIV-1 infection in highly pre-treated children from 2 to 12 years of age with virus resistant to multiple PI.

The Marketing Authorisation Holder (MAH) has submitted a group of type II variations to update the sections 4.3, 4.4 and 4.5 of the SmPC with information on pharmacokinetics interaction with alfuzocin, sildenafil, colchicine, salmeterol, bosentan, raltegravir and valaciclovir.

In addition, the MAH took the opportunity to introduce minor linguistic changes to the French, Greek, Italian, Portuguese, Spanish, Finnish, German, Hungarian and English annexes and to update the details of the Spanish local representative in the package leaflet. A sentence about elderly patients is deleted from the package leaflet of oral solution presentation. Annex II has been updated according to the latest QRD recommendations.

The variations submitted in the group are the following:

Variations requested		**Type**
C.I.4	Variations related to significant modifications of the SmPC due in particular to new quality, pre-clinical, clinical or	II

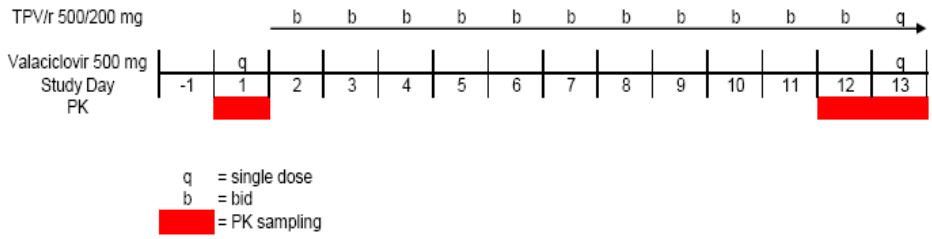
Variations requested		Type
	pharmacovigilance data	

1.2. Clinical aspects

Concomitant use of Valaciclovir

Within this application, the MAH submitted the results of a pharmacokinetic study (study 1182.104) to document the interaction between tipranavir/ritonavir (TPV/r) and valaciclovir (VAL).

This study was an open-label one-sequence cross-over pharmacokinetic interaction study of steady-state TPV/r 500/200 mg with single-dose VAL (500 mg) in healthy volunteers. The table below describes the design of study 1182.104.

Study title	An open-label one-sequence cross-over pharmacokinetic interaction study of steady-state tipranavir/ritonavir 500/200 mg with single-dose valaciclovir (500 mg) in healthy volunteers
Phase	1
Methodology	Open label, one-sequence, cross over, pharmacokinetic study in healthy male and female HIV-negative adult volunteers
Number of subjects	enrolled: 29; entered: 29; evaluated: 26 actual**:** enrolled: 29; entered: 29; analysed: 29 (safety set); 26 (primary endpoint)
Criteria for inclusion	Healthy female and male subjects, age > 19 and < 59 years (20 to 58 years inclusive), weight ≥ 60 kg, BMI > 18.5 and < 29.9 kg/m2;
Study design	
Criteria for evaluation	Primary endpoints: AUC0-12h and Cmax for VAL Secondary endpoints: - AUC0-12h , Cmax and C12h (or Clast) for TPV and RTV - CL/F, VZ/F and t½ for VAL, TPV and RTV - Safety
Statistical methods	Two-sided 90% confidence intervals (CIs) for the median of intra-subject ratios of AUC0-12h and Cmax were calculated to determine whether the CIs are contained in the acceptance range of 80-125%. Additionally, the corresponding point estimators (geometric means) for the median intra-subject ratios and the associated confidence intervals were provided.

Pharmacokinetics results

29 subjects (25 males and 4 females) were randomised and treated and a total of 26 subjects completed the trial as planned. For safety reasons, 3 subjects prematurely discontinued the treatment

during treatment with TPV/r due to AEs. These patients developed Development of Acquired Immune Deficiency Syndrome (DAIDS) Grade 3 or Grade 4 rapidly increasing ALT and/or AST elevations which occurred between day 7 and day 8 of the study.

The effect of steady-state TPV/r 500/200 mg bid on VAL Cmax and AUC0-12h is summarised in the table presented below.

PK Parameter	Treatment	Geometric Mean	Geometric Mean Ratio C:A	SE[1]	90% Confidence Interval	p-value for ratio outside of [0.8, 1.25]
Cmax (µg/mL)	A: VAL	3.722	0.951	1.044	[0.883, 1.023]	0.0002
	C: VAL + TPV/r	3.538				
AUC_{0-12h} (h•µg/mL)	A: VAL	10.970	1.061	1.015	[1.035, 1.088]	< 0.0001
	C: VAL + TPV/r	11.641				
$AUC_{0-\infty}$ (h•µg/mL)	A: VAL	11.476	1.066	1.014	[1.041, 1.092]	< 0.0001
	C: VAL + TPV/r	12.235				
C_{p12h} (µg/mL)	A: VAL	0.123	1.189	1.039	[1.113, 1.269]	0.1009
	C: VAL + TPV/r	0.147				

[1] Standard Error

The effect of single-dose VAL on the steady-state pharmacokinetics of TPV 500 mg (co-administered with RTV 200 mg) is summarised below.

PK Parameter	Treatment	Geometric Mean	Geometric Mean Ratio C:B	SE[1]	90% Confidence Interval	p-value for ratio outside of [0.8, 1.25]
Cmax (µM)	B: TPV/r	124.438	1.023	1.042	[0.954, 1.097]	<0.0001
	C: VAL + TPV/r	127.286				
AUC_{0-12h} (h•µM)	B: TPV/r	833.415	1.010	1.030	[0.960, 1.062]	< 0.0001
	C: VAL + TPV/r	841.484				
C_{p12h} (µM)	B: TPV/r	28.197	0.981	1.034	[0.926, 1.039]	< 0.0001
	C: VAL + TPV/r	27.654				

[1] Standard Error

The effect of single-dose VAL on the steady-state pharmacokinetics of RTV 200 mg (co-administered with TPV 500 mg) is summarised in the table below.

PK Parameter	Treatment	Geometric Mean	Geometric Mean Ratio C:B	SE[1]	90% Confidence Interval	p-value for ratio outside of [0.8, 1.25]
Cmax (µg/mL)	B: TPV/r	1.946	0.806	1.075	[0.712, 0.913]	0.4588
	C: VAL + TPV/r	1.569				
AUC_{0-12h} (h•µg/mL)	B: TPV/r	7.079	0.860	1.052	[0.789, 0.938]	0.0814
	C: VAL + TPV/r	6.090				
C_{p12h} (µg/mL)	B: TPV/r	0.070	0.943	1.074	[0.834, 1.065]	0.0150
	C: VAL + TPV/r	0.066				

[1] Standard Error

Safety data

There were 4 serious adverse events (SAEs) in 2 subjects and 1 other significant AE in 1 subject, all of which leading to discontinuation of treatment. Two subjects were withdrawn due to elevated ALT and one subject due to elevated ALT and AST, which were described as toxic hepatitis.

A total of 24 out of 29 subjects experienced an AE during the trial. By comparing the different treatment periods, most AEs occurred during TPV/r treatment (23 out of 29 subjects),

Overall, 70 AEs were recorded during the study period, of which 60 AEs were assessed to be drug-related. While the majority of the documented AEs was of mild intensity (45 AEs), some of the recorded AEs were of moderate (11 AEs) or severe intensity (14 AEs). Among the 14 AEs of severe intensity, for 8 subjects elevated ALT values and for 4 subjects elevated AST values were recorded.

The pattern of AEs observed in this study was consistent with that seen in previous phase I healthy volunteer trials with VAL administration or TPV/r.

The most frequently observed drug-related AEs were increases of ALT and AST as to expect for TPV and RTV co-medication from previous clinical trials. VAL has a well established AE profile, which includes mostly headaches and gastrointestinal tract symptoms which were additional, more frequently observed drug-related AEs. All subjects who experienced an AE during the study recovered fully.

According to the MAH, co-administration of steady-state TPV/r 500/200 mg bid with single-dose VAL 500 mg did not affect VAL Cmax or AUC (less than a 10% change relative to VAL alone), but was associated with an 18.9% increase in the concentration of VAL measured 12 h after VAL dosing (Cp12h). Tipranavir Cmax, Cp12h and AUC0-12h were unaffected by VAL (less than a 10% change relative to TPV/r alone). A single dose of VAL had no effect on RTV Cp12h (less than a 10% decrease relative to TPV/r alone), but was associated with a 19.4% decrease in Cmax and a 14.0% decrease in AUC0-12h. None of these changes were considered to be of clinical relevance by the MAH.

Based on these results, The MAH has proposed to include in section 4.5 of the SmPC under "Interactions-CYP Isoenzyme Inhibitors" section a statement that no dose adjustment is needed when administering TPV/r with VAL.

Concomitant use of raltegravir

The MAH presented results from the following publication: "*Effect of tipranavir-ritonavir on pharmacokinetics of raltegravir; Hanley D et al; Antimicrobial agents and chemotherapy, July 2009, p. 2752–2755 Vol. 53, No. 7.*"

Raltegravir (RAL) is an integrase inhibitor that is used in combination with other antiretroviral agents, potentially including protease inhibitors, in the treatment of antiretroviral-naïve and experienced HIV-infected patients. RAL is predominantly eliminated through glucuronidation via the UGT 1A1 isozyme, which it neither inhibits nor induces. RAL is not a cytochrome P450 (CYP) 3A4 substrate and, thus, it does not affect CYP3A4 metabolism. RAL is a substrate of the efflux transporter P-glycoprotein (P-gp) and has been shown not to inhibit it.

The abstract of this article is presented below:

Raltegravir (RAL) is a novel and potent human immunodeficiency virus type 1 integrase inhibitor that is predominantly metabolized via glucuronidation. The protease inhibitor combination tipranavir (TPV) at 500 mg and ritonavir (RTV) at 200 mg (TPV-RTV) has inhibitory and inductive effects on metabolic enzymes, which includes the potential to induce glucuronosyltransferase. Because RAL may be coadministered with TPV-RTV, there is the potential for the induction of RAL metabolism. Consequently, we assessed the effect of TPV-RTV on the pharmacokinetics of RAL and the safety and tolerability of this combination. Eighteen healthy adults were enrolled in this open-label study. The participants received RAL at 400 mg twice daily for 4 days (period 1) and TPV-RTV twice daily for 7 days (period 2), followed immediately by 400 mg RAL with TPV-RTV twice daily for 4 days (period 3). Under steady-state conditions, the RAL concentration at 12 h (C12) was decreased when RAL was administered with TPV-RTV (geometric mean ratio [GMR], 0.45; 90% confidence interval [CI] 0.31, 0.66; P = 0.0021); however, the area under the concentration-time curve from time zero to 12 h (GMR, 0.76; 90% CI, 0.49, 1.19; P = 0.2997) and the maximum concentration in serum (GMR, 0.82; 90% CI, 0.46, 1.46; P = 0.5506) were not substantially affected. There were no serious adverse experiences or discontinuations due to study drug-related adverse experiences, and RAL coadministered with TPV-RTV was generally well tolerated. Although the RAL C12 was decreased with TPV-RTV in this study, favorable efficacy data collected in phase III studies substantiate that TPV-RTV may be coadministered with RAL without dose adjustment.

Based on this information, the MAH proposed to add a statement in section 4.5 of the SmPC under "Interactions - Integrase strand transfer inhibitor" that no dosage adjustment is recommended concerning co-administration of TPV/r with RAL.

Additional information on pharmacokinetics interactions

Following a request of FDA, the US SmPC of Aptivus was recently updated with new safety information relatives to drug-drug interactions between Aptivus and a list of medicinal products: sildenafil, alfuzosin, salmeterol, tadalafil, bosentan and colchicine.

Through the current application, the MAH proposed to update the European SmPC and Package Leaflet of Aptivus in order to take into account these drug-drug interactions, except for the interaction with tadalafil which is already addressed in the European SmPC.

Interaction with PDE-5 inhibitors

Tipranavir is a substrate, an inducer and an inhibitor of cytochrome P450 CYP3A. When coadministered with ritonavir at the recommended dosage there is a net inhibition of P450 CYP3A.

PDE-5 inhibitors (sildenafil, tadalafil and vardenafil) are metabolised by CYP3A4.

A safe and effective dose has not been established when PDE-5 inhibitors are used with TPV/r. There is increased potential for PDE-5 inhibitors-associated adverse events (which include visual disturbances, hypotension, prolonged erection, and syncope).

The co-administration of TPV/r with drugs which are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events are contraindicated. As these drugs include sildenafil when used for the treatment of pulmonary arterial hypertension (PAH), the MAH proposed to update section 4.3 of the SmPC 'Contraindications' to contraindicate the use of sildenafil in PAH. The MAH also proposed to include a statement about sildenafil in section 4.5 'Interaction with other medicinal products and other forms of interaction' of the SmPC mentioning a safe and effective dose has not been established when used with TPV/r.

Interaction with alfuzosin

Alfuzosin is an alpha-1 receptor antagonist used in the management of hypertension and benign prostatic hypertrophy. Alfuzosin is partially metabolised and excreted mainly in the bile and faeces. None of the metabolites found in man has any pharmacodynamic activity. CYP3A4 is the principal hepatic enzyme isoform involved in the metabolism of alfuzosin.

Based on theoretical considerations, co-administration of TPV with low dose RTV and alfuzosin results in increased alfuzosin concentrations and may result in hypotension.

As the co-administration of TPV/r with drugs which are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events are contraindicated, the MAH proposed to update sections 4.3 'Contraindications' and 4.5 'Interaction with other medicinal products and other forms of interaction' of the SmPC to include information about this pharmacokinetic interaction and contraindicate the use of alfuzosin.

Interaction with colchicine

Based on theoretical considerations, colchicine concentrations may increase upon co-administration with TPV and low dose RTV.

Therefore, the MAH proposed to update sections 4.4 'Special warnings and precautions for use' and 4.5 'Interaction with other medicinal products and other forms of interaction' of the SmPC with additional information concerning concomitant use of colchicine and recommend a reduced dosing when co-administered with TPV/r.

Interaction with salmeterol

With regards to salmeterol, the combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia. Therefore, the MAH proposed to update section 4.4 'Special warnings and precautions for use' and 4.5 'Interaction with other medicinal products and other forms of interaction' of the SmPC to include a statement that concomitant administration with salmeterol is not recommended.

Interaction with bosentan

Bosentan is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension. Bosentan is metabolised by and is also an inducer of CYP2C9 and 3A4. Based on

theoretical considerations, bosentan concentrations may increase upon co-administration with TPV and low dose RTV. The MAH proposed to update section 4.5 'Interaction with other medicinal products and other forms of interaction' of the SmPC to recommend a reduced dosing when co-administered with TPV/r.

Discussion

With regards to interactions between TPV/r and VAL, the MAH conclusion and proposed update of the product information is considered acceptable by the CHMP.

Regarding interactions with RAL, the MAH concluded '*raltegravir concentrations were decreased when administered with TPV/r but this did not result in a substantial change in the AUC. Therefore it is concluded that TPV-RTV may be co administered with RAL without dose adjustment*'. However, the conclusion of the authors of the publication mentions '*In conclusion, multiple doses of TPV-RTV decreased the RAL C12, although AUC0–12 and Cmax were not substantially affected. Favourable efficacy data collected in phase III substantiate that TPV-RTV may be coadministered with RAL without a dose adjustment*'. Therefore, the CHMP recommended a different wording from the one proposed by the MAH to be included in the SmPC for sake of accuracy (please refer to the below section on changes to the product information). In addition, when applicable, the CHMP requested the MAH to reflect the changes in relevant PK parameters with arrows and as geometric mean change (%), according to annexe A of the EMA Guideline on the clinical development of medicinal products for the treatment of HIV infection.

Considering that the use of PDE-5 inhibitors in general (out of pulmonary hypertension) leads to caution in dose initiation, the CHMP considered appropriate to indicate that no dose can be recommended with Aptivus boosted with low dose of ritonavir. However, the CHMP recommended the additional paragraph should not be limited to sildenafil.

The MAH's proposal relative to alfuzocin was considered acceptable by CHMP.

The MAH's proposal for a reduced posology of colchicine when co-administered with tipranavir/ritonavir was based on the use of 0.6 mg colchicine-containing tablets. However, in Europe authorised formulations may vary across member states and could for example contain 1 mg of colchicine. However, beyond these dosage considerations, it appears that clinically severe interactions are more and more involving colchicine. The mechanism goes probably through P-gp and possibly also involves CYP3A4. Therefore, the CHMP recommended that concomitant administration should be not recommended, knowing that in some very rare cases (periodic disease), colchicine may have to be given the life long. In most cases, the concomitant use with TPV/r, and more generally with all PIs, should be strongly discouraged.

With regards to interaction with salmeterol, although the safety margin of salmeterol appears quite high, the CHMP considered appropriate that the coadministration of TPV/r with salmeterol should be discouraged.

The CHMP also considered that the proposal of a reduced dosing for bosentan in case of co-administration with APT/r was not substantiated. First of all, the MAH should refer to the statement included in the EU SmPC for Tracleer (bosentan) which gives the results of an interaction study in healthy volunteers co-administered with LPV/r and Tracleer. Initial plasma through concentration of bosentan was increased by 48-fold. However, the SmPC does not recommend reducing the dose of bosentan. Moreover, the MAH did not discuss to what extent this results could be extrapolated to drug-drug interaction between tipranavir boosted (TPV/rtv) and bosentan, due to the complicated metabolism of TPV. At last, the possibility of additive hepatotoxicity of bosentan as well as that of

TPV/rtv is an issue of particular concern and warrants a more discouraging statement, i.e. a not recommended combination, as stated in the Tracleer SmPC for another hepatotoxic antiretroviral agent (e.g. nevirapine). Consequently, the MAH was requested to revisit the proposed statement by stating that "due to a marked hepatotoxicity of bosentan that could cumulate with TPV/rtv liver toxicity, this combination is not recommended".

Changes to the product information

In accordance with the above discussion, the Aptivus product information is updated as follows (addition underlined).

Section 4.3 'Contraindications'

'…

Also contraindicated is the use of the alpha-1 adrenoceptor antagonist alfuzosin, and sildenafil when used for the treatment of pulmonary arterial hypertension.

…'

Section 4.4 'Special warnings and precautions for use'

'*Colchicine:*

The administration of colchicine and APTIVUS, co-administered with low dose ritonavir, is not recommended. (see section 4.5).

Salmeterol:

Concomitant use of salmeterol and APTIVUS, co-administered with low dose ritonavir, is not recommended (see section 4.5).

Bosentan:

Due to the marked hepatotoxicity of bosentan and the potential for increasing the liver toxicity associated with APTIVUS,co-administered with low dose ritonavir, this combination is not recommended.'

Section 4.5 'Interaction with other medicinal products and other forms of interaction'

Integrase strand transfer inhibitors		
Raltegravir *400 mg BID*	*Raltegravir Cmax ↔* *Raltegravir AUC 0-12↔* *Raltegravir C12: ↓ 45%* *Despite an almost half reduction of C12, previous clinical studies with this combination did not evidence an impaired outcome.* *The mechanism of action is thought to be induction of glucuronosyltransferase by tipranavir/r.*	*No particular dose adjustment is recommended.*

Anti-gouts		
Colchicine	*Based on theoretical considerations, colchicine concentrations may increase upon co-administration with tipranavir and low dose ritonavir.* *Colchicine is a substrate of CYP3A4 and P-gp (an intestinal efflux transporter).*	*The administration of APTIVUS with low dose ritonavir and colchicine is not recommended.*

Endothelin receptor antagonists		
Bosentan	*Based on theoretical considerations, bosentan concentrations may increase upon co-administration with tipranavir and low dose ritonavir.* *Inhibition of CYP 3A4 by tipranavir/r*	*Co-administration of bosentan and APTIVUS with low dose ritonavir is not recommended. (see section 4.4)*

Inhaled beta agonists		
Salmeterol	*The concurrent administration of tipranavir and low dose ritonavir may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.* *Inhibition of CYP 3A4 by tipranavir/r.*	*Concurrent administration of APTIVUS, co-administered with low dose ritonavir, is not recommended.*

Phosphodiesterase 5 (PDE5) inhibitors		
Sildenafil ***Vardenafil*** *No interaction study performed*	*Co-administration of tipranavir and low dose ritonavir with PDE5 inhibitors is expected to substantially increase PDE5 concentrations and may result in an increase in PDE5 inhibitor-associated adverse events including hypotension, visual changes and priapism.* *CYP 3A4 inhibition by tipranavir/ r*	*Particular caution should be used when prescribing the phosphodiesterase (PDE5) inhibitors sildenafil or vardenafil in patients receiving APTIVUS, co-administered with low dose ritonavir.* *A safe and effective dose has not been established when used with APTIVUS, co-administered with low dose ritonavir. There is increased potential for PDE5 inhibitor-associated adverse events (which include visual disturbances, hypotension, prolonged erection, and syncope).*
Tadalafil *10 mg QD*	*Tadalafil first-dose Cmax ↓ 22%* *Tadalafil first-dose AUC ↑ 133%* *CYP 3A4 inhibition and induction by tipranavir/r* *Tadalafil steady-state Cmax ↓ 30%* *Tadalafil steady-state AUC ↔*	*It is recommended to prescribe tadalafil after at least 7 days of APTIVUS with ritonavir dosing.* *A safe and effective dose has not been established when used with APTIVUS, co-administered with low dose ritonavir. There is increased potential for PDE5 inhibitor-associated adverse events (which*

	No clinically significant change is observed in tipranavir PK parameters.	*include visual disturbances, hypotension, prolonged erection, and syncope).*

Nucleoside analogue DNA polymerase inhibitors		
Valaciclovir *500 mg single dose*	*Co-administration of valaciclovir, tipranavir and low dose ritonavir was not associated with clinically relevant pharmacokinetic effects.* *Tipranavir: ↔* *Valaciclovir: ↔*	*Valaciclovir and APTIVUS with low dose ritonavir, may be co-administered without dose adjustment.*
Alpha 1-adrenoreceptor antagonists		
Alfuzosin	*Based on theoretical considerations, co-administration of tipranavir with low dose ritonavir and alfuzosin results in increased alfuzosin concentrations and may result in hypotension.* *CYP 3A4 inhibition by tipranavir/r*	*The concomitant use of APTIVUS, co-administered with low dose ritonavir, with alfuzosin is contraindicated.*

Package Leaflet

` *Do NOT take APTIVUS*

if you are currently taking products containing:

- alfuzosin and sildenafil (when used to treat a rare blood vessel disorder characterized by increased pressure in the pulmonary artery).'

The following medications are not recommended:

- salmeterol (used to achieve long-term asthma control, bronchospasm prevention with COPD).

- colchicine (used to treat gout flares)

- bosentan (used to treat pulmonary artery hypertension).'

In addition, the MAH took the opportunity to introduce minor linguistic changes to the French, Greek, Italian, Portuguese, Finnish, German, Hungarian, Spanish and English annexes and to update the details of the Spanish local representative in the package leaflet.

Annex II has also been updated according to the latest QRD recommendations.

A sentence about elderly patients was deleted from the package leaflet of Aptivus oral solution presentation as it was added by mistake during the renewal phase.

The CHMP endorsed these product information updates.

2. Conclusion

On 19 May 2011, the CHMP considered this group of Type II variations to be acceptable and agreed on the amendments to be introduced in the SmPC, Annex II and Package Leaflet.