Aptivus

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion / Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
IAIN/0080	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/09/2018		SmPC	
N/0079	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/06/2018		Labelling and PL	
IA/0078	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the	23/05/2018	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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	product information				
PSUSA/2973/ 201612	Periodic Safety Update EU Single assessment - tipranavir	14/09/2017	10/11/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2973/201612.
IB/0077	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/07/2017		SmPC and Labelling	
IA/0075	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	15/03/2017	n/a		
IA/0074	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	15/08/2016	n/a		
IB/0072/G	This was an application for a group of variations. B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of	08/04/2016	n/a		

	specification limits B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)				
IB/0073	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/02/2016	06/02/2017	SmPC, Annex II and PL	
N/0071	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/11/2015	06/02/2017	Labelling	
R/0070	Renewal of the marketing authorisation.	23/04/2015	19/06/2015	SmPC and PL	
IB/0069/G	This was an application for a group of variations. B.II.a.3.a.1 - Changes in the composition (excipients) of the finished product - Changes in components of the flavouring or colouring system - Addition , deletion or replacement B.II.e.1.a.2 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Semi-solid and non-sterile liquid pharmaceutical forms B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	17/09/2014	n/a		

	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information				
PSUV/0067	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
II/0062/G	This was an application for a group of variations. Grouping of an application to update section 4.5 of the SmPC with information on emtricitabine and an application to update sections 4.3, 4.4, 4.5 of the SmPC with information on products undergoing cytochrome P450 (CYP) 3A metabolism (i.e. cobicistat and cobicistat-containing products, etravirine, rilpivirine, boceprevir, telaprevir) and new information on CYP3A metabolized products already listed in the interaction section (i.e. atorvastatin, sildenafil, colchicine). The PL is updated accordingly. In addition, editorial changes have been introduced. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/06/2014	06/08/2014	SmPC and PL	New information on the drug drug interactions with emtricitabine, cobicistat and cobicistat-containing products, etravirine, rilpivirine, boceprevir, telaprevir was added to the product information. In addition, the existing information in the product information on the drug drug interactions with atorvastatin, sildenafil, colchicine was updated. No new interaction study was performed by the MAH. The proposed changes mirror the data mentioned in the SmPC of the drugs concerned or are based on theoretical considerations. The co-administration of colchicine with Aptivus/ritonavir is contraindicated in patients with renal or hepatic impairment; however, a reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treated with Aptivus/ritonavir.

IB/0068	To update SmPC section 4.4 and the Package Leaflet with new information on the risk of HIV transmission as requested by the CHMP for all HIV medicines. Based on new data available the recommendation for post-exposure prophylaxis should be updated. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/07/2014	19/06/2015	SmPC and PL	
IG/0432	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	16/04/2014	n/a		
II/0064	Update of section 4.8 of the SmPC in line with the recent MedDRA version 16.0 terminology, the PL has been updated accordingly. Update to section 4.7 of the SmPC to harmonise the information already included in the PL. Changes to the SmPC, Annex II and PL in line with the latest QRD template version 9. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/02/2014	06/08/2014	SmPC, Annex II and PL	The tabulated summary of adverse reactions in section 4.8 of the SmPC was updated in line with the revision of MedDRA (MedDRA version 16.0): “loose stools” changed to “diarrhea” (frequency unchanged), “muscle cramp” renamed “muscle spasm”, “renal insufficiency” renamed “renal failure”. A recommendation of caution when driving a car or operating machinery was added in section 4.7 of the SmPC.
IA/0065	A.7 - Administrative change - Deletion of manufacturing sites	27/01/2014	n/a		
II/0060	Update of sections 4.3 and 4.5 of the SmPC to include information regarding quetiapine following a class labelling for all HIV protease inhibitors. The PL was updated accordingly. In addition, the MAH took the	21/11/2013	18/12/2013	SmPC and PL	Please refer to the Assessment Report: Aptivus-H-C-631-II-60

	opportunity to add Croatia to the list of local representatives in the PL. Furthermore, minor linguistic changes (linguistic corrections) were introduced to the German/Austrian, Italian and Spanish product information. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IA/0063/G	This was an application for a group of variations. B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	10/12/2013	n/a		
IA/0061/G	This was an application for a group of variations. B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure B.II.e.3.a - Change in test procedure for the	10/12/2013	06/08/2014	SmPC	

	immediate packaging of the finished product - Minor changes to an approved test procedure				
IB/0059	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	24/05/2013	18/12/2013	SmPC and PL	To include in SmPC sections 4.4 and 4.8 information regarding autoimmune disorders under Immune Reactivation Syndrome, following a class labelling for all antiretrovirals as requested by the CHMP. The changes have also been reflected in the PL.
IB/0058/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/03/2013	18/12/2013	SmPC, Annex II, Labelling and PL	To update the product information (SmPC, Annex 11, Labelling and Package Leaflet) of Aptivus soft capsules and oral solution according to the updated QRD template (version 8.3) and to harmonise the Package Leaflet to the SmPC in order to be compliant with the QRD template. Further, the MAH takes the opportunity to implement minor linguistic changes to the Finnish, French, German/Austrian, Greek and Italian product information.
IG/0211	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/09/2012	n/a		
N/0056	"The MAH updated the list of local representatives contact details for BE, LU, DK, DE, EE, RO and LV, and made corrections in section 4 (Possible side effects) and section 2 (before you take/your child takes Aptivus) of the package leaflets. The MAH also took the opportunity to make minor linguistic amendments in the English, French and Spanish package leaflets." Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/07/2012	18/12/2013	PL	

WS/0255/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of the Description of Pharmacovigilance System (DDPS). C.I.9.z - Changes to an existing pharmacovigilance system as described in the DDPS - Other variation C.I.9.z - Changes to an existing pharmacovigilance system as described in the DDPS - Other variation C.I.9.f - Changes to an existing pharmacovigilance system as described in the DDPS - Deletion of topics covered by written procedure(s) describing pharmacovigilance activities C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	24/05/2012	24/05/2012		Changes to an existing pharmacovigilance system as described in the DDPS. The MAH update the Detailed Description of the Pharmacovigilance System (DDPS) for Aptivus, MicardisPlus, Mirapexin, Onduarp, Pradaxa, Sifrol, Trajenta, Twynsta and Viramune.
IA/0054	B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	29/03/2012	n/a		
IA/0053	B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change	12/03/2012	n/a		

	to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State				
II/0052	Update of section 4.8 of the SmPC to align this section with the SmPC guideline as requested by CHMP further to the assessment of PSUR 8. The MAH also took the opportunity to implement minor linguistic changes to the French and Maltese Annexes. Annex II is also updated in line with the latest QRD template and to reflect that the PSUR cycle follows the standard requirements. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	17/11/2011	19/12/2011	SmPC and Annex II	Further to the assessment of PSUR 8 covering the period from 01 January 2010 to 31 December 2010 and in light of the guideline on Summary of Product Characteristics (SmPC) section 4.8 of the SmPC has been revised in order to provide physicians with more comprehensive information. As part of this revision, the frequency of the adverse reaction intracranial haemorrhage has been revised to 'rare' based on an updated estimation considering patients included in clinical trials and compassionate use.
IB/0051/G	This was an application for a group of variations. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a	29/07/2011	n/a		

	test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method				
II/0050	Update of the SmPC section 5.1 with the results of a clinical study assessing the electrophysiological effects of tipranavir co-administered with ritonavir. In	19/05/2011	29/06/2011	SmPC and PL	The clinical study submitted was designed as a single-centre, randomised, placebo-controlled, double-blind, two-way crossover trial with two parallel dose groups. The effect of

	addition, the MAH has modified for clarity a statement relative to the risk of passing HIV in the product information (section 4.4 of the SmPC and package leaflet) as per CHMP request. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				tipranavir with low dose of ritonavir on the QTcF interval was measured in 81 healthy subjects receiving the following treatments twice daily for 2.5 days: tipranavir/ritonavir (500/200 mg), tipranavir/ritonavir at a supra-therapeutic dose (750/200 mg), and placebo/ritonavir (-/200 mg). After baseline and placebo adjustment, the maximum mean QTcF change was 3.2 ms (1-sided 95% Upper CI: 5.6 ms) for the 500/200 mg dose and 8.3 ms (1-sided 95% Upper CI: 10.8 ms) for the supra-therapeutic 750/200 mg dose. Hence tipranavir at therapeutic dose with low dose of ritonavir did not prolong the QTc interval but may do so at supratherapeutic dose.
II/0049/G	This was an application for a group of variations. Update of the SmPC sections 4.3, 4.4 and 4.5 and package leaflet with information on interaction of tipranavir/ritonavir with raltegravir, valaciclovir, sildenafil, alfuzosin, salmeterol, bosentan and colchicine. 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. A sentence about elderly patients was deleted from the package leaflet of oral solution presentation. Annex II has been updated according to the latest QRD recommendations. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/05/2011	29/06/2011	SmPC, Annex II and PL	Please refer to the Assessment Report: Aptivus-H-C-631-II-49-G

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
R/0047	Renewal of the marketing authorisation.	22/07/2010	05/10/2010	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of Aptivus continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Aptivus continues to be favourable. The CHMP recommends the renewal of the Marketing Authorisation for Aptivus but requires an additional five-year renewal on the basis of pharmacovigilance grounds with regard to hepatotoxicity events and blood disorders including blood coagulation parameters and intracranial haemorrhage cases.
IA/0048/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	09/08/2010	n/a		

	B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State				
IB/0041/G	This was an application for a group of variations. B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material	21/05/2010	n/a		
IA/0046/G	This was an application for a group of variations. B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method	15/04/2010	n/a		

	B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
IA/0045/G	This was an application for a group of variations. B.I.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method B.I.c.2.c - Change in the specification parameters and/or limits of the immediate packaging of the AS - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.c.3.a - Change in test procedure for the immediate packaging of the AS - Minor changes to an approved test procedure	15/04/2010	n/a		
IA/0044	B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition	15/04/2010	n/a		
IA/0043	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	15/04/2010	n/a		
IA/0042	A.7 - Administrative change - Deletion of manufacturing sites	15/04/2010	n/a		
IA/0040	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	11/01/2010	n/a		

IA/0039	IA_13_a_Change in test proc. for active substance - minor change	11/01/2010	n/a		
II/0036	Update of section 4.5 "Interaction with other medicinal products and other forms of interactions" of the Summary of Product Characteristics in line with the annex A of the revised Guideline on the clinical development of medicinal products for the treatment of HIV infection (CPMP/EWP/633/02, Rev. 2), including addition of new data concerning the co-administration of tipranavir with the proton pump inhibitors (FU2 059.1) and rosuvastatin/pravastatin (FU2 018.2). Consequently to update of 4.5 the section 4.4 "Special warnings and precautions for use" is updated concerning the co-administration with proton pump inhibitors and the co-administration with statins. In addition the MAH took the opportunity to update Section 4.2 "Posology and method of administration" with a recommendation in case of missed dose. The package leaflet was updated accordingly. The MAH also amended the contact details of the local representative in Romania, Slovenia, Slovak Republic Hungary ands Netherlands and revised the Finnish set of annexes according to the new QRD Template. Update of Summary of Product Characteristics and Package Leaflet	22/10/2009	23/11/2009	SmPC and PL	The full section 4.5 of the SPC has been formatted into a table with three columns for each product co-administered with tipranavir/ritonavir (TPV/r) in accordance with the guideline (CPMP/EWP/633/02, Rev. 2). The description of the interactions data follows a single pattern for all medicinal products co-administered with TPV which increases the legibility and facilitates the use of the interaction section for the treating physician as outlined in the guidance. Pharmacokinetics data and recommendations to treating physician are supported by clinical studies already submitted by the MAH and assessed by the CHMP at the time of the original marketing authorisation application or subsequently during the lifecycle of TPV through clinical Follow-Up Measures and type II variation procedures. As a consequence of the addition of information on rosuvastatin and pravastatin in section 4.5, section 4.4 on co-administration with statins is updated to reinforce the recommendations of careful monitoring by informing to initiate treatment at the lowest dose and by making a cross reference to section 4.5. As a consequence of the addition of information on pantoprazole, lansoprazole and rabeprazole in section 4.5 section 4.4 is updated to reinforce the guidance to not recommend the combined used of TPV/r with either omeprazole or esomeprazole by extending it to other PPIs. In order to further improve treatment compliance the recommendation in case of missed dose has been added in section 4.2. If a dose of TPV/r is missed by more than 5 hours, the patient should wait and then take the next dose of

					TPV/r at the regularly scheduled time. If the dose is missed by less than 5 hours, the patient should take the dose immediately and take the next dose of TPV/r at the regularly scheduled time. This is based on the half-life of TPV in the presence of RTV and the recommended dosing interval of approximately 5 hours used in most TPV clinical trials.
II/0037	Update of Detailed Description of the Pharmacovigilance System (DDPS). Consequently, Annex II has been updated with the new version number. Update of DDPS (Pharmacovigilance)	24/09/2009	16/10/2009	Annex II	The DDPS has been updated to version 5.2 to reflect the change of the Qualified Person for Pharmacovigilance (QPPV) as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS.
N/0038	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/09/2009	n/a	Labelling	
X/0030	Annex I_2.(d) Change or addition of a new pharmaceutical form	23/04/2009	23/06/2009	SmPC, Labelling and PL	
II/0029	Extension of indication to include the treatment of HIV-1 infection in highly pre-treated adolescents 12 years of age or older with virus resistant to multiple protease inhibitors. Extension of Indication	23/04/2009	23/06/2009	SmPC, Annex II, Labelling and PL	Please note that this assessment report will be published after deletion of commercial confidential information.
II/0035	Update of section 4.5 of the SPC to include information on the interaction between TPV co-administered with ritonavir and buprenorphine/naloxone from results of the clinical study 1182.85.	23/04/2009	29/05/2009	SmPC	Study 1182.85 assessed the effect of steady-state tipranavir/ritonavir (TPV/r) twice daily on the steady-state pharmacokinetics of buprenorphine/naloxone. The active metabolite norbuprenorphine presented decreased pharmacokinetic parameters (about -80%) when

	Update of Summary of Product Characteristics				co-administered with TPV/r. This may result in decreased clinical efficacy of buprenorphine. Therefore, patients should be monitored for opiate withdrawal syndrome.
II/0032	Update of section 4.5 of the SPC to include information on the increased tipranavir levels associated with co-administration of tipranavir/ritonavir and enfuvirtide following the CHMP conclusion dated 30 May 2007 on PSUR 3. Update of Summary of Product Characteristics	22/01/2009	02/03/2009	SmPC	During the review of PSUR 3 a potential interaction between tipranavir and enfuvirtide was suspected from 13 case reports which involved a hepatic event whilst the patients were on a tipranavir/ritonavir/enfuvirtide (TPV/r/ENF) combination. In 2006, Requena et al also described this interaction where co-administration of TPV/r with ENF resulted in an increase in TPV and RTV plasma trough concentrations of approximately 50%. At last, in the RESIST trials, higher TPV trough plasma levels were observed in patients receiving TPV/r with ENF compared to patients not receiving ENF (45% higher). The increase in plasma concentrations occurred within the first two weeks of combination. These findings cannot be explained by the metabolic profile of the medicinal products. No information was available for AUC and Cmax parameters. Clinical data available from the RESIST trials did not suggest any significant alteration of the tipranavir/ritonavir safety profile when combined with enfuvirtide as compared to patients treated with tipranavir/ritonavir without enfuvirtide.
II/0033	Update of section 4.5 of the SPC to include information on interaction between tipranavir/ritonavir and bupropion. Section 2 of the PL was updated accordingly. In addition the MAH took the opportunity to update the contact details of the Austrian MAH local representative. Update of Summary of Product Characteristics and Package Leaflet	20/11/2008	22/12/2008	SmPC and PL	The results of the study 1182.95 showed that co-administration of tipranavir/ritonavir with bupropion resulted in potentially clinically significant reductions in Ctrough, Cmax and AUC of bupropion (60%, 44% and 49%, respectively) without significant changes in Tmax and T1/2. Co-administration of tipranavir/ritonavir with bupropion also resulted in 24-25% decreases in the Ctrough, Cmax and AUC for the active metabolite hydroxybupropion. The half-life of hydroxybupropion was substantially reduced by

					approximately 58%. This reduction is likely due to induction of CYP2B6 and UGT activity by ritonavir, and possibly due to induction of CYP3A4 by tipranavir/ritonavir. As the maximum recommended dose of bupropion (300 mg / day) should not be increased to compensate for this induction effect, the combination should be avoided. However, if the co-administration with bupropion is considered unavoidable, close clinical monitoring for bupropion efficacy is necessary.
II/0034	Update of section 4.3 and section 4.5 of the SPC to implement the class labelling text agreed by the CHMP in May 2008 on the combination of rifampicin with tipranavir given with concomitant low-dose ritonavir. Update of Summary of Product Characteristics	25/09/2008	21/10/2008	SmPC	In 2005 an interaction study on saquinavir boosted with ritonavir together with rifampicin in healthy volunteers had to be prematurely discontinued due to an increased risk of hepatotoxicity associated with this co-administration. The mechanism for this interaction is not fully elucidated. It has been hypothesised that the predominant effect between the inducer effect of rifampicin and the inhibitor effect of the boosted protease inhibitors might depend on the boosted protease inhibitor involved. Lacking the results of specific interaction studies, the CHMP concluded as a conservative measure to reinforce the contraindication with rifampicin in section 4.4 and improve the guidance provided to physicians regarding the interaction of boosted protease inhibitors with rifampicin in section 4.5.
IA/0031	IA_05_Change in the name and/or address of a manufacturer of the finished product	16/07/2008	n/a		
II/0023	Update of sections 4.4 and 5.3 of the SPC to include results from non-clinical studies for tipranavir-related effects on coagulation parameters and to advise caution for the co-administration of high doses of vitamin E. Section 2 of the PL was updated accordingly.	30/05/2008	07/07/2008	SmPC and PL	Following reports of intracranial hemorrhage during clinical trials, studies were conducted in male rats to explore the effects of tipranavir (TPV) on coagulation. Bleeding events were observed, associated with prolonged prothrombin time (PT), activated partial thromboplastin time (aPTT) and a decrease in some vitamin K dependent factors.

	Update of Summary of Product Characteristics and Package Leaflet				Co-administration of tipranavir with vitamin E-TPGS, an esterified derivative of vitamin E, resulted in an exacerbation of the anti-coagulant effects of TPV in male rats, specifically causing increases in PT, aPTT, and Thrombotest levels and decreases in vitamin K dependent factors. Co-administration of tipranavir with vitamin E should be used with caution and at doses not higher than 1200 IU vitamin E per day.
S/0027	Annual re-assessment.	21/02/2008	22/04/2008	SmPC, Annex II, Labelling and PL	In view of the submitted efficacy and safety data, the CHMP concluded that the benefit risk balance of ritonavir-boosted tipranavir in the treatment of adult patients with virus resistant to multiple protease inhibitors remains positive. As all remaining Specific Obligations were fulfilled, the CHMP agreed that exceptional circumstances should be lifted.
II/0028	Update of section 4.4 and 4.5 of the SPC with information on the interaction between tipranavir/ritonavir and omeprazole. Section 2 of the PL has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	21/02/2008	27/03/2008	SmPC and PL	In contrast to observations with other Protease Inhibitors, no clinically significant effect on tipranavir plasma concentrations after co-administration with omeprazole was seen. Based on this information no dose adjustment of tipranavir/ritonavir in case of co-administration would be required. However, a clinically important effect on omeprazole concentrations was observed. Omeprazole exposure was decreased by about 70% in the presence of steady-state tipranavir/ritonavir. Due to the uncertainty of the effectiveness of such lowered concentrations of omeprazole in patients, this combination is therefore not recommended. Nevertheless, for those patients in need of proton-pump-inhibitor therapy and without reasonable alternatives, omeprazole might be used. This will necessitate appropriate omeprazole dose increases and clinical evaluation of the patient's response to therapy and, if

					necessary, further dose-alteration, depending on response.
II/0026	Update of section 5.3 of the SPC based on the CHMP's assessment in June 2007 of in vitro studies showing effects of tipranavir on thromboxane synthase, thromboxane A2, thrombin and PAF binding. Update of Summary of Product Characteristics	15/11/2007	19/12/2007	SmPC	Tipranavir was found to inhibit platelet aggregation when testing human platelets and thromboxane A2 binding in an in vitro cell model at levels consistent with exposure observed in patients receiving Aptivus/ritonavir. The clinical implications of these findings are not known. The currently known effects of Aptivus/ritonavir on bleeding are already reflected in section 4.4 of the SPC.
II/0025	Update of section 4.5 of the SPC based on a pharmacokinetic drug-drug interaction study between efavirenz and tipranavir/ritonavir. Furthermore, the MAH clarified the wording on interaction with nevirapine. In addition, the MAH took this opportunity to update the Product Information in line with the EMEA/QRD template version 7.2. Update of Summary of Product Characteristics, Labelling and Package Leaflet	20/09/2007	22/10/2007	SmPC, Annex II, Labelling and PL	The submitted study showed that the Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) efavirenz, co-administered with tipranavir/ritonavir at the currently recommended and approved dosages, did not significantly alter the pharmacokinetics of tipranavir and/or ritonavir. Moreover, it was confirmed that efavirenz plasma concentration was not modified by tipranavir/ritonavir. Due to the absence of significant interaction between efavirenz and tipranavir/ritonavir observed in the submitted study, and taking into account previous data provided by the MAH on the nevirapine-tipranavir/ritonavir interaction, a significant drug-drug interaction between nevirapine and tipranavir/ritonavir seems unlikely to occur. The information in section 4.5 of the SPC on the interaction of tipranavir/ritonavir and both NNRTIs efavirenz and nevirapine was updated accordingly.
II/0022	Update of section 4.5 of the SPC based on in vitro mechanistic studies assessing P-gp and PXR induction as requested by the CHMP in November 2006 following the assessment of Follow-up measure 005.	20/09/2007	22/10/2007	SmPC	Based on the results of in vitro studies, tipranavir seems to be a substrate and also an inhibitor of P-glycoprotein (P-gp). Consequently, it is possible that interactions between tipranavir and

	Update of Summary of Product Characteristics				P-gp could affect the absorption, distribution and excretion of other drugs that interact with P-gp when administered concomitantly with tipranavir/ritonavir (TPV/r). At this time, the most reliable method to study the ability for a drug to induce Cytochrome P (CYP) is to quantify the enzyme activity of primary hepatocyte cultures. It has been shown in vitro that tipranavir is a CYP3A4 inducer but only mildly induces P-gp, MRP2 (Multidrug resistance Protein 2) and UGT1A1 (Uridine glucuronosyltransferase 1A1). Based on these results, the data related to P-gp induction by tipranavir in the current section 4.5 of Aptivus SPC was updated.
II/0024	Update of section 4.5 of the SPC based on a clinical study report assessing the effects of single dose and steady state tipranavir/ritonavir on the single dose pharmacokinetics of tadalafil and as requested by the CHMP on 26 April 2007. Update of Summary of Product Characteristics	20/09/2007	15/10/2007	SmPC	In comparing the pharmacokinetic profile of tadalafil prior to tipranavir/ritonavir and with the first dose of tipranavir/ritonavir, there was a clinically important increase in tadalafil exposure. However, for tipranavir/ritonavir administration at steady-state, there was essentially no change in tadalafil except for the Cmax that was decreased. Although there were no important safety findings observed in the clinical trial, the increase in the tadalafil exposure seen with the first dose of tipranavir/ritonavir administration suggests that the increase in tadalafil exposure might alter the tadalafil safety profile. Therefore, the use of tadalafil should be avoided during the first 7-10 days of tipranavir/ritonavir dosing. After steady-state is achieved with tipranavir/ritonavir, tadalafil can be administered without dose modification.
II/0021	Update of sections 4.4 and 4.5 of the SPC based on a study assessing the steady state pharmacokinetics of carbamazepine (200mg or 100mg twice daily depending on tolerability) administered alone or in combination with tipranavir/ritonavir after a single	24/05/2007	02/07/2007	SmPC and PL	This study demonstrated that the co-administration of tipranavir/ritonavir (TPV/RTV) with carbamazepine (CBZ) 200 mg twice daily led to an increased exposure of CBZ and of its active metabolite by about 20 %, however no significant effect was observed with CBZ 100 mg twice daily.

	dose and at steady state. The Package Leaflet is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				It could also be extrapolated that higher doses of CBZ may result in larger decreases in TPV plasma concentrations, which may further lead to reduced antiviral efficacy. Therefore, the CHMP considered that caution is required when co-administering TPV/RTV with high doses of CBZ. Additionally, the statement in section 4.5 of the SPC includes phenobarbital and phenytoin, as they are, like CBZ, also inducers of CYP3A4. The PL is updated accordingly.
II/0017	Update of sections 4.3, 4.4 and 4.5 of the SPC to include information on interactions of tipranavir/ritonavir with transporters and CYP isoenzymes based on the results of a human pharmacokinetic study as requested by the CHMP in July 2005. Consequently, the PL is updated as well. Update of Summary of Product Characteristics and Package Leaflet	24/05/2007	02/07/2007	SmPC and PL	The presented "Cocktail study" uses a methodology which is a tool to test the drug interaction profile of a substance. It is a phenotyping tool for screening potential drug-drug interactions when an active compound has got an effect on several metabolism-involved enzymes and transporters. To this end, a "Cocktail" of either isozyme or transporter specific biomarkers is administered in healthy human volunteers who are given the active under investigation (here tipranavir/r) as well. The results of this study are summarised as such: Over the first few doses of TPV/r moderate inhibition of CYP1A2 and CYP2C9 occurred, moderate inhibition of p-glycoprotein occurred and potent inhibition of CYP2D6 and hepatic and intestinal CYP3A occurred. Intestinal P-glycoprotein and CYP3A activity were more profoundly affected than hepatic P-glycoprotein and CYP3A activity. Prolonged TPV/r exposure induced the activity of CYP1A2, CYP2C9, hepatic and intestinal P- glycoprotein, and hepatic and intestinal CYP3A, whereas prolonged exposure further inhibited CYP2D6 activity. At steady-state, modest net induction of CYP1A2 and CYP2C9 occurred, and potent inhibition of CYP2D6 and hepatic and intestinal CYP3A

					occurred. The net effect on P-glycoprotein, as measured by digoxin, was decreased compared to baseline conditions.
II/0008	Update of sections 4.1 and 5.1, subsection "Analyses of tipranavir resistance in treatment experienced patients" of the SPC based on the data on the impact of mutations on the virological response to tipranavir/ritonavir observed at 48 weeks in the two pivotal clinical trials. This follows a request by the CHMP on 27 April 2006 further to the assessment of the submitted clinical trial data and their corresponding meta-analysis. Update of Summary of Product Characteristics	26/04/2007	04/06/2007	SmPC	The analysis of resistance data from RESIST-1 and -2 trials showed that treatment and virological response at week 48 was superior in the tipranavir/ritonavir arm than in the comparator arm in both pivotal clinical trials. However, the analysis also showed clearly that the magnitude of response was to a very high degree dependant on the use of enfuvirtide for the first time in the optimised background regimen. Additionally, the analysis showed that mutations on the protease gene that also occur with the use of other, more widely used protease inhibitors may lead to loss of virological response during tipranavir treatment. Therefore, a sentence was added in section 4.1 to draw special attention to the need for careful evaluation of a patient's genotype prior to initialisation of tipranavir/ritonavir. A regression analysis was performed to determine which mutation score was most predictive of virological and therapeutic response in patients participating in the RESIST-1 and -2 trials. As this analysis proved the so called tipranavir mutation score to be the most relevant, it is now reflected in the SPC to allow treating physicians to make the most informed choice on starting tipranavir treatment based on genotyping of their patients.
IB/0020	IB_17_a_Change in re-test period of the active substance	16/04/2007	n/a		
S/0012	1st annual re-assessment	24/01/2007	21/03/2007	SmPC, Annex II, Labelling and PL	In view of the submitted efficacy and safety data, the CHMP concluded that the benefit risk balance of ritonavir-boosted tipranavir in the treatment of adult patients with virus resistant to multiple protease inhibitors remains positive.

					As there are still remaining Specific Obligations, the CHMP agreed that the Marketing Authorisation should remain under exceptional circumstances.
II/0018	Update of section 5.3 of the SPC with results of two-year carcinogenicity studies in rats and mice as requested by the CHMP. Update of Summary of Product Characteristics	24/01/2007	27/02/2007	SmPC	The studies showed that tipranavir is a rat and mouse carcinogen with the augmentation of liver and thyroid tumours. These tumours are likely due to the fact that tipranavir is an enzyme inducer leading to liver hyperplasia and augmentation of the clearance of thyroid hormones. Such mechanisms of liver and thyroid tumours observed in rodents have been observed with several chemicals and it is unlikely that this effect would occur in humans.
II/0016	Update of section 4.4 of the SPC to reflect the results of an in vitro platelet aggregation assays. Update of Summary of Product Characteristics	24/01/2007	27/02/2007	SmPC	The in vitro assays performed in human and rat plasma showed that tipranavir inhibits platelet aggregation. This indicates that there may be a weak anti-platelet effect at concentrations achieved in clinical practice. This study only tested the in vitro ability of tipranavir to inhibit platelet aggregation. It is unknown whether this effect also would occur in vivo and if this effect is reversible or not. This will be undergoing further investigations.
II/0015	Update of sections 4.2 and 4.4 of SPC based on the analysis of resistance data from a 48 week clinical study in treatment naïve patients. A warning not to use Aptivus in the treatment of antiretroviral naïve patients was introduced. Consequentially, the PL was updated. Update of Summary of Product Characteristics and Package Leaflet	24/01/2007	27/02/2007	SmPC and PL	The data presented from a clinical trial in antiretroviral naïve patients showed that tipranavir/ritonavir should not be used in this patient population. This conclusion was based on the fact that in the treatment arm where tipranavir was given together with 200mg ritonavir twice daily as currently approved for experienced patients, the safety profile was unfavourable as compared to the comparator arm (lopinavir/ritonavir) without having additional benefits. Therefore, this arm was closed prematurely. In the second tipranavir arm where ritonavir was given at 100mg twice

					daily, the safety profile was more favourable. However, non-inferiority could not be shown to the comparator. Consequently, this arm was stopped as well. Tipranavir/ritonavir should not be used in antiretroviral naïve patients, as the benefit risk balance in this population was found to be negative.
II/0010	Update of section 4.4 of the SPC to amend the liver function test (LFT) monitoring schedules and the criteria for rechallenge, as requested by the CHMP in March 2006. Update of Summary of Product Characteristics	24/01/2007	27/02/2007	SmPC	Hepatotoxicity is one of the major concerns as regards the safety profile of tipranavir/ritonavir used at the indicated dose of 500/200 mg twice daily. To minimise this risk in clinical practice, the liver function test monitoring was reviewed. In consequence, the frequency of liver function testing was increased, specifically during the initiation period of treatment. Additionally, a recommendation to discontinue tipranavir/ritonavir as soon as any sings of liver damage appear was added.
II/0014	To update section 4.8 of the SPC and section 4 of the PL by adding information on hyperbilirubinaemia following the assessment of the first quarterly report of fatalities and hepatic disorders. Update of Summary of Product Characteristics and Package Leaflet	14/12/2006	24/01/2007	SmPC and PL	"Hyperbilirubinemia" with three reports and "blood bilirubin increased" with another two reports were unlisted hepatic terms that had been reported more than once within the first quarterly safety review covering the period 1 January to 31 March 2006. Both hyperbilirubinaemia and increased levels of blood bilirubin had not been reported more than once in the reference data set of 1397 patients; therefore, it was assigned to the frequency category rare (<1/1000).
II/0013	Update of sections 4.4 and 4.8 of the SPC and section 2 of the PL to implement the class labelling text on osteonecrosis, agreed by the CHMP in September 2006. Section 6 of the PL was updated with the local representatives in Bulgaria and Romania and in	14/12/2006	24/01/2007	SmPC and PL	Cases of osteonecrosis (death of the bone tissue resulting from an insufficient blood supply) have been reported in HIV-infected patients since the end of the 80's. Although the cause of this disease could be due to multiple factors (including the use of corticosteroids, alcohol consumption, severe immunosuppression, higher body mass index) it has occurred specially in patients with HIV advanced disease

	Belgium and Luxembourg. Update of Summary of Product Characteristics and Package Leaflet				and/or in patients with long term use of combination antiretroviral therapy (CART). Further to the review of all available data the CHMP agreed that this information should now be included in the SPC and PL of all antiretroviral medicinal products. Patients should be warned to seek medical advice in case they experience joint stiffness, aches and pain especially of the hip, knee and shoulder or if they experienced any difficulty in movement.
II/0011	Update of section 4.5 of the Aptivus SPC with information on the potential interaction between tipranavir/ritonavir and trazodone further to the assessment of a pharmacokinetic study between ritonavir and trazodone published in the literature. Relevant sections of the PL are amended in accordance. Update of Summary of Product Characteristics and Package Leaflet	18/10/2006	24/11/2006	SmPC and PL	In a pharmacokinetic study performed in 10 healthy volunteers, the concomitant use of ritonavir (at a lower dose of 200mg) with one dose of trazodone led to an increase in the blood plasma levels of trazodone. Three patients experienced adverse events, such as dizziness, nausea, hypotension, bradycardia, pallor and syncope. It is unknown whether tipranavir/ritonavir may cause an even larger increase in the levels of trazodone. Therefore, the combination of these medicinal products should be used with caution, including a possible need for dose adjustments. This information was included in the interaction section of the SPC and reflected in the PL as well.
II/0009	Update of section 5.1 subsection "Antiviral activity in vitro" of the Aptivus SPC to add the results of recently performed studies measuring the in vitro activity of tipranavir on HIV-1 group M and group O clades and on HIV-2 isolates. Update of Summary of Product Characteristics and Package Leaflet	18/10/2006	24/11/2006	SmPC and PL	Based on two in vitro studies, investigating the antiretroviral activity of tipranavir against HIV-1 group M and O clades as well as HIV-2 isolates section 5.1 of the SPC was updated to reflect the fact that tipranavir shows antiretroviral activity in vitro against all of the tested sub-types. However, interpretation of results in the HIV-1 group O and HIV-2 isolates were complicated by the lack of a suitably validated assay for the determination of the inhibitor concentration leading to 50% inhibition of viral replication (EC50). Furthermore, additional information on in vitro results on the interaction of tipranavir with other antiretroviral medicinal

					products was removed from this section of the SPC in light of the clinical data already reflected elsewhere in the SPC.
II/0007	Update of sections 4.4 and 4.8 of the Aptivus SPC to include information explaining the risk of intracranial haemorrhage (ICH), based upon cases observed in Aptivus clinical trials. This follows the CHMP's assessment of a cumulative review by the MAH on haemorrhage events, especially intracranial bleeding, which was endorsed on 28 June 2006. Consequentially, section 4 of the Package Leaflet is updated as well. Update of Summary of Product Characteristics and Package Leaflet	27/07/2006	28/08/2006	SmPC and PL	Further to preclinical data where rats exposed to tipranavir experienced bleedings and based on a cumulative review provided by the MAH, the CHMP concluded that there is a signal for increased rates of intracranial haemorrhage (ICH) in tipranavir/ritonavir-exposed patients. The rate of ICH in tipranavir-exposed patients appears to be higher than the ones seen in the nevirapine and enfuvirtide clinical development programs but in the range of the rate reported in the literature from clinical cohorts of HIV-infected persons. In many of the tipranavir/ritonavir-exposed patients, a plausible alternative explanation for the ICH was noted on review of the individual case reports. However, in the six remaining cases of the case-by-case analysis, the role of tipranavir/ritonavir in the ICH event could not be excluded. Due to the serious nature of these ICH events with an expected mortality rate of approximately 50% these findings require further evaluation. The added wording to the SPC and PL reflects the current state of knowledge and is well accompanied by the Dear Doctor Letter to inform prescribers about this safety signal. The benefit risk balance for tipranavir remains favourable, although all bleeding adverse events must be carefully monitored and all findings should be cumulatively presented in future PSURs.
II/0006	Addition of the information on the interaction profile in the case of co-administration of tipranavir with the protease inhibitor atazanavir into sections 4.4 and 4.5 of the Aptivus SPC, as requested by the CHMP on 27	27/07/2006	28/08/2006	SmPC and PL	Although, the combination of tipranavir/ritonavir (500/100 mg twice daily) with atazanavir (300 mg once daily) appeared to be at least as tolerable as atazanavir/ritonavir alone in this healthy volunteer population, coadministration

	April 2006 further to the assessment of the report for a clinical study, assessing the PK interaction between steady-state tipranavir/ritonavir at single dose and steady-state atazanavir. Consequently, Section 2 of the PL is also amended. Update of Summary of Product Characteristics and Package Leaflet				of tipranavir/ritonavir (500/100 mg twice daily) with atazanavir (300 mg once daily) is not recommended. This is due to the PK interaction of the combination leading to a significant reduction in atazanavir levels, as well as substantial increase of tipranavir and ritonavir exposure. Therefore, the co-administration of atazanavir and tipranavir should be strictly discouraged. It cannot be excluded that the effects of the medicinal products on each other would be more pronounced if they were to be administered at both their recommended dosages (tipranavir/ritonavir 500/200 mg twice daily & atazanavir/ritonavir 300/100 mg once daily). Therefore, further studies to explore dose adjustments would be very difficult to handle and are not recommended.
II/0005	Addition of information concerning the effects of methadone within the paragraph "Narcotic analgesics" (Methadone/Meperidine) in section 4.5 of the Aptivus Summary of Product Characteristics as requested by the CHMP on 3 May 06 further to the assessment of the report of a clinical study assessing the PK interaction between tipranavir/ritonavir at steady state and methadone. Update of Summary of Product Characteristics	27/07/2006	28/08/2006	SmPC	Co-administration of single-dose methadone with tipranavir/ritonavir resulted in a decrease in methadone exposure in fasted healthy volunteers. The pharmacokinetics data in the study suggest that patients treated with methadone co-administered with tipranavir/ritonavir require monitoring for clinical symptoms of withdrawal from methadone and may require an increased dose of methadone. The steady-state tipranavir exposure decreased as well when methadone was co-administered with steady-state tipranavir/ritonavir.
II/0003	Update of section 4 of the PL to include the list of uncommon and rare adverse reactions as defined in section 4.8 of the SPC. Update of Package Leaflet and Labelling	23/02/2006	29/03/2006	PL	The proposed additions to the PL harmonise the information on uncommon and rare adverse reactions with that of section 4.8 in the SPC. The potential risks of tipranavir therapy are thereby better and more accurately described and accessible by the patients.

IA/0004	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	10/01/2006	n/a		
II/0001	Update of section 4 of the PL with the information on the occurrence of hepatitis and hepatic failure (hepatotoxicity) in line with sections 4.4 and 4.8 of the SPC. Update of Package Leaflet and Labelling	30/11/2005	23/12/2005	PL	The liver toxicity is a major concern with tipranavir. Therefore the CHMP agreed in his opinion on the granting of a marketing authorisation for Aptivus under exceptional cirmcumstances during September 2005 CHMP on introducing strong warnings and stringent monitoring of liver tests prior and during treatment as specified in the Summary of Product Characteristics. The proposed wording in the PL corresponds to the information already included within section 4.8 "Undesirable Effects" of the SPC, in which hepatitis and hepatic failure (including fatal outcome) are listed as expected adverse reactions, under the frequency category 'uncommon' and 'rare', respectively. Furthermore, the advice to be observant for signs and symptoms of hepatitis reflects the advice already given in section 4.4 "Special Warnings and Precautions for Use" of the SPC. Addition of this information to the PL clearly highlights and more accurately informs the patient of the potential risk of hepatitis and hepatic failure. The potential risk to all patients, not just those higher risk patients with baseline prognostic factors, is thereby better and more accurately described.
IA/0002	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	05/12/2005	n/a		