ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Aptivus 250 mg soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 250 mg tipranavir.

Excipients with known effect: Each soft capsule contains
100.0 mg ethanol, 455.0 mg macrogolglycerol ricinoleate and 12.6 mg sorbitol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule.

Pink, oblong soft gelatin capsules imprinted with "TPV 250" in black.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aptivus, co-administered with low dose ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infection in highly pre-treated adults and adolescents 12 years of age or older with virus resistant to multiple protease inhibitors. Aptivus should only be used as part of an active combination antiretroviral regimen in patients with no other therapeutic options.

In deciding to initiate treatment with Aptivus, co-administered with low dose ritonavir, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of Aptivus. Initiation of treatment should take into account the combinations of mutations which may negatively impact the virological response to Aptivus, co-administered with low dose ritonavir (see section 5.1).

4.2 Posology and method of administration

Aptivus must always be given with low dose ritonavir as a pharmacokinetic enhancer, and in combination with other antiretroviral medicinal products. The Summary of Product Characteristics of ritonavir must therefore be consulted prior to initiation of therapy with Aptivus (especially as regards the contraindications, warnings and undesirable effects sections).

Aptivus should be prescribed by physicians who are experienced in the treatment of HIV-1 infection.

Posology
Adults and adolescents (from 12 – 18 years of age)
The recommended dose of Aptivus is 500 mg, co-administered with 200 mg ritonavir (low dose ritonavir), twice daily (see section 4.4 for precautionary measures in adolescents).

Doses of ritonavir lower than 200 mg twice daily should not be used as they might alter the efficacy profile of the combination.
Since currently only limited efficacy and safety data are available for adolescents (see section 5.1) close monitoring of virologic response and tolerance is particularly warranted in this patient group.

Missed dose
Patients should be advised of the need to take Aptivus and ritonavir every day as prescribed. If a dose is missed by more than 5 hours, the patient should be instructed to wait and then to take the next dose of Aptivus and ritonavir at the regularly scheduled time. If a dose is missed by less than 5 hours, the patient should be instructed to take the missed dose immediately, and then to take the next dose of Aptivus and ritonavir at the regularly scheduled time.

Elderly
Clinical studies of Aptivus did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects (see section 5.2).
In general, caution should be exercised in the administration and monitoring of Aptivus in older people reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other therapy (see section 4.4).

Liver impairment
Tipranavir is metabolised by the hepatic system. Liver impairment could therefore result in an increase of tipranavir exposure and a worsening of its safety profile. Therefore, Aptivus should be used with caution, and with increased monitoring frequency, in patients with mild hepatic impairment (Child-Pugh Class A). Aptivus is contraindicated in patients with moderate or severe (Child-Pugh Class B or C) hepatic impairment (see sections 4.3, 4.4 and 5.2).

Renal impairment
No dosage adjustment is required in patients with renal impairment (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of Aptivus capsules in children aged 2 to 12 years has not been established. Currently available data are described in section 5.1 and 5.2 but no recommendation on a posology can be made.

Also, appropriate dose adjustments for children under 12 years cannot be achieved with Aptivus capsules. Aptivus oral solution is available for children between 2 and 12 years of age (please refer to the respective SmPC for further details).

The safety and efficacy of Aptivus in children under 2 years of age has not been established. No data are available.

Method of administration
Oral use.
Aptivus soft capsules co-administered with low dose ritonavir should be taken with food (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients with moderate or severe (Child-Pugh B or C) hepatic impairment.

Combination of rifampicin with Aptivus with concomitant low dose ritonavir is contraindicated (see section 4.5).

Herbal preparations containing St John's wort (*Hypericum perforatum*) due to the risk of decreased plasma concentrations and reduced clinical effects of tipranavir (see section 4.5).

Co-administration of Aptivus with low dose ritonavir, with active substances that are highly dependent on CYP3A for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These active substances include antiarrhythmics (such as amiodarone, bepridil, quinidine), antihistamines (such as astemizole, terfenadine), ergot derivatives (such as

dihydroergotamine, ergonovine, ergotamine, methylergonovine), gastrointestinal motility agents (such as cisapride), antipsychotics (such as pimozide, sertindole, quetiapine), sedatives/hypnotics (such as orally administered midazolam and triazolam) and HMG-CoA reductase inhibitors (such as simvastatin and lovastatin) (see section 4.5). Also the use of the alpha-1 adrenoceptor antagonist alfuzosin, and sildenafil when used for the treatment of pulmonary arterial hypertension. In addition, co-administration of Aptivus with low dose ritonavir, and medicinal products that are highly dependent on CYP2D6 for clearance, such as the antiarrhythmics flecainide, propafenone and metoprolol given in heart failure (see section 4.5).

Co-administration of colchicine with Aptivus/ritonavir in patients with renal or hepatic impairment (see section 4.5).

4.4 Special warnings and precautions for use

Aptivus must be administered with low dose ritonavir to ensure its therapeutic effect (see section 4.2). Failure to correctly co-administer tipranavir with ritonavir will result in reduced plasma levels of tipranavir that may be insufficient to achieve the desired antiviral effect. Patients should be instructed accordingly.

Aptivus is not a cure for HIV-1 infection or AIDS. Patients receiving Aptivus or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV-1 infection.

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Switching from Aptivus capsules to the oral solution
Aptivus capsules are not interchangeable with the oral solution. Compared to the capsules, tipranavir exposure is higher when administering the same dose as oral solution. Also, the composition of the oral solution is different from that of the capsules, with the high vitamin E content being especially noteworthy. Both of these factors may contribute to an increased risk of adverse reactions (type, frequency and/or severity). Therefore patients should not be switched from Aptivus capsules to Aptivus oral solution (see sections 5.1 and 5.2).

Switching from Aptivus oral solution to the capsules
Aptivus oral solution is not interchangeable with the capsules. Compared to the oral solution, tipranavir exposure is lower when administering the same dose as capsules. However, children previously treated with Aptivus oral solution and becoming 12 years of age should be switched to capsules, particularly because of the more favourable safety profile of the capsules. It has to be noted that the switch from the oral solution to the capsule formulation of Aptivus could be associated with decreased exposure. Therefore, it is recommended that patients switching from Aptivus oral solution to capsules at the age of 12 years are closely monitored for the virologic response of their antiretroviral regimen (see sections 5.1 and 5.2).

Liver disease
Aptivus is contraindicated in patients with moderate or severe (Child-Pugh Class B or C) hepatic insufficiency. Limited data are currently available for the use of Aptivus, co-administered with low dose ritonavir, in patients co-infected with hepatitis B or C. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reaction. Aptivus should be used in this patient population only if the potential benefit outweighs the potential risk, and with increased clinical and laboratory monitoring. In the 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 mild hepatic impairment (Child-Pugh Class A) should be closely monitored.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination therapy and should be monitored according to standard practice. Aptivus with ritonavir should be discontinued once signs of worsening liver function occur in patients with pre-existing liver disease.

Aptivus co-administered with low dose ritonavir, has been associated with reports of clinical hepatitis and hepatic decompensation, including some fatalities. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medicinal products. Caution should be exercised when administering Aptivus to patients with liver enzyme abnormalities or with a history of hepatitis. Increased ALAT/ASAT monitoring should be considered in these patients.

Aptivus therapy should not be initiated in patients with pre-treatment ASAT or ALAT greater than 5 times the Upper Limit Normal (ULN) until baseline ASAT/ALAT is stabilised at less than 5X ULN, unless the potential benefit justifies the potential risk.

Aptivus therapy should be discontinued in patients experiencing ASAT or ALAT elevations greater than 10X ULN, or developing signs or symptoms of clinical hepatitis during therapy. If another cause is identified (eg acute hepatitis A, B or C virus, gallbladder disease, other medicinal products), then rechallenge with Aptivus may be considered when ASAT/ALAT have returned to the patient's baseline levels.

Liver monitoring
Monitoring of hepatic tests should be done prior to initiation of therapy, after two, four and then every four weeks until 24 weeks, and then every eight to twelve weeks thereafter. Increased monitoring (i.e. prior to initiation of therapy, every two weeks during the first three months of treatment, then monthly until 48 weeks, and then every eight to twelve weeks thereafter) is warranted when Aptivus and low dose ritonavir are administered to patients with elevated ASAT and ALAT levels, mild hepatic impairment, chronic hepatitis B or C, or other underlying liver disease.

Treatment-naïve patients
In a study performed in antiretroviral naïve adult patients, tipranavir 500 mg with ritonavir 200 mg twice daily, as compared to lopinavir/ritonavir, was associated with an excess in the occurrence of significant (grade 3 and 4) transaminase elevations without any advantage in terms of efficacy (trend towards a lower efficacy). The study was prematurely stopped after 60 weeks.
Therefore, tipranavir with ritonavir should not be used in treatment-naïve patients (see section 4.2).

Renal impairment
Since the renal clearance of tipranavir is negligible, increased plasma concentrations are not expected in patients with renal impairment.

Haemophilia
There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthrosis in patients with haemophilia type A and B treated with protease inhibitors. In some patients additional Factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship has been evoked, although the mechanism of action had not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Bleeding
RESIST participants receiving Aptivus with ritonavir tended to have an increased risk of bleeding; at 24 weeks the relative risk was 1.98 (95% CI=1.03, 3.80). At 48-weeks the relative risk decreased to 1.27 (95% CI=0.76, 2.12). There was no pattern for the bleeding events and no difference between treatment groups in coagulation parameters. The significance of this finding is being further monitored.

Fatal and non-fatal intracranial haemorrhages (ICH) have been reported in patients receiving Aptivus, many of whom had other medical conditions or were receiving concomitant medicinal products that

may have caused or contributed to these events. However, in some cases the role of Aptivus cannot be excluded. No pattern of abnormal haematological or coagulation parameters has been observed in patients in general, or preceding the development of ICH. Therefore, routine measurement of coagulation parameters is not currently indicated in the management of patients on Aptivus.

An increased risk of ICH has previously been observed in patients with advanced HIV disease/AIDS such as those treated in the Aptivus clinical trials.

In *in vitro* experiments, tipranavir was observed to inhibit human platelet aggregation at levels consistent with exposures observed in patients receiving Aptivus with ritonavir.

In rats, co-administration with vitamin E increased the bleeding effects of tipranavir (see section 5.3).

Aptivus, co-administered with low dose ritonavir, should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other medical conditions, or who are receiving medicinal products known to increase the risk of bleeding such as antiplatelet agents and anticoagulants or who are taking supplemental vitamin E. Based on the limits of exposure available from observation in clinical trials, it is recommended not to co-administer to patients more than 1,200 IU vitamin E per day.

Diabetes mellitus/hyperglycaemia
New onset of diabetes mellitus, hyperglycaemia or exacerbations of existing diabetes mellitus has been reported in patients receiving antiretroviral therapy, including protease inhibitors. In some of these the hyperglycaemia was severe and in some cases also associated with ketoacidosis. Many of the patients had confounding medical conditions, some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycaemia.

Lipid elevations
Treatment with Aptivus co-administered with low dose ritonavir and other antiretroviral agents has resulted in increased plasma total triglycerides and cholesterol. Triglyceride and cholesterol testing should be performed prior to initiating tipranavir therapy and during therapy. Treatment-related lipid elevations should be managed as clinically appropriate.

Fat redistribution
Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV infected patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors, and lipoatrophy and nucleoside reverse transcriptase inhibitors, has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with factors related to the active substance such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

Immune reactivation syndrome
In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and pneumocystis pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. In addition, reactivation of herpes simplex and herpes zoster has been observed in clinical studies with Aptivus, co-administered with low dose ritonavir.

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Rash
Mild to moderate rashes including urticarial rash, maculopapular rash, and photosensitivity have been reported in subjects receiving Aptivus, co-administered with low dose ritonavir. At 48-weeks in Phase III trials, rash of various types was observed in 15.5% males and 20.5% females receiving Aptivus co-administered with low dose ritonavir. Additionally, in one interaction trial, in healthy female volunteers administered a single dose of ethinyl oestradiol followed by Aptivus co-administered with low dose ritonavir, 33% of subjects developed a rash. Rash accompanied by joint pain or stiffness, throat tightness, or generalized pruritus has been reported in both men and women receiving Aptivus co-administered with low dose ritonavir. In the paediatric clinical trial, the frequency of rash (all grades, all causality) through 48 weeks of treatment was higher than in adult patients.

Osteonecrosis
Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Interactions
The interaction profile of tipranavir, co-administered with low dose ritonavir, is complex. The mechanisms and potential mechanisms contributing to the interaction profile of tipranavir are described (see section 4.5).

Abacavir and zidovudine
The concomitant use of Aptivus, co-administered with low dose ritonavir, with zidovudine or abacavir, results in a significant decrease in plasma concentration of these nucleoside reverse transcriptase inhibitors (NRTIs). Therefore, the concomitant use of zidovudine or abacavir with Aptivus, co-administered with low dose ritonavir, is not-recommended unless there are no other available NRTIs suitable for patient management (see section 4.5).

Protease inhibitors
Concomitant use of Aptivus, co-administered with low dose ritonavir, with the protease inhibitors amprenavir, lopinavir or saquinavir (each co-administered with low dose ritonavir) in a dual-boosted regimen, results in significant decreases in plasma concentrations of these protease inhibitors. A significant decrease in plasma concentrations of atazanavir and a marked increase of tipranavir and ritonavir concentrations was observed when Aptivus, associated with low dose ritonavir, was co-administered with atazanavir (see section 4.5). No data are currently available on interactions of tipranavir, co-administered with low dose ritonavir, with protease inhibitors other than those listed above. Therefore, the co-administration of tipranavir, co-administered with low dose ritonavir, with protease inhibitors is not recommended.

Oral contraceptives and oestrogens
Since levels of ethinyl oestradiol are decreased, the co-administration of Aptivus co-administered with low dose ritonavir is not recommended. Alternative or additional contraceptive measures are to be used when oestrogen based oral contraceptives are co-administered with Aptivus co-administered with low dose ritonavir (see section 4.5). Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency. Women using oestrogens may have an increased risk of non serious rash.

Anticonvulsants
Caution should be used when prescribing carbamazepine, phenobarbital, and phenytoin. Aptivus may be less effective due to decreased tipranavir plasma concentrations in patients taking these agents concomitantly.

Halofantrine, lumefantrine
Due to their metabolic profile and inherent risk of inducing torsades de pointes, administration of halofantrine and lumefantrine with Aptivus co-administered with low dose ritonavir, is not recommended.

Disulfiram/metronidazole
Aptivus soft capsules contain alcohol (7% ethanol, ie 100 mg per capsule or up to 200 mg per dose) which can produce disulfiram-like reactions when co-administered with disulfiram or other medicinal products which produce this reaction (e.g. metronidazole).

Fluticasone
Concomitant use of tipranavir, co-administered with low dose ritonavir, and fluticasone or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see section 4.5).

Atorvastatin
Tipranavir, co-administered with low dose ritonavir, increases the plasma concentrations of atorvastatin (see section 4.5). The combination is not recommended. Other HMG-CoA reductase inhibitors should be considered such as pravastatin, fluvastatin or rosuvastatin (see section 4.5). However, if atorvastatin is specifically required for patient management, it should be started with the lowest dose and careful monitoring is necessary.

Omeprazole and other proton pump inhibitors
The combined use of Aptivus with ritonavir with either omeprazole, esomeprazole or with other proton pump inhibitors is not recommended (see section 4.5).

Colchicine
In patients with normal renal and hepatic function, a reduction in colchicine dosage or an interruption of colchicine treatment is recommended in co-administration (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.

Warnings related to certain excipients
Due to Aptivus containing small amounts of sorbitol, patients with rare hereditary problems of fructose intolerance should not take this medicine.

Aptivus contains macrogolglycerol ricinoleate which may cause stomach upset and diarrhoea.

This medicinal product contains 7 vol % ethanol (alcohol), i.e. up to 400 mg per daily dose, equivalent to 8 ml of beer, or less than 4 ml of wine. Harmful for those suffering from alcoholism.
To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.

4.5 Interaction with other medicinal products and other forms of interaction

The interaction profile of Aptivus, co-administered with low dose ritonavir, is complex and requires special attention in particular in combination with other antiretroviral agents.

Interaction studies have only been performed in adults.

Metabolic profile of tipranavir

Tipranavir is a substrate, an inducer and an inhibitor of cytochrome P450 CYP3A. When co-administered with ritonavir at the recommended dosage (see section 4.2) there is a net inhibition of P450 CYP3A. Co-administration of Aptivus and low dose ritonavir with agents primarily metabolised by CYP3A may result in changed plasma concentrations of tipranavir or the other agents, which could alter their therapeutic and undesirable effects (see list and details of considered agents, below). Agents that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse reactions are detailed in this section, and listed in section 4.3.

A cocktail study was conducted in 16 healthy volunteers with twice-daily 500 mg tipranavir with 200 mg ritonavir capsule administration for 10 days to assess the net effect on the activity of hepatic CYP 1A2 (caffeine), 2C9 (warfarin), 2D6 (dextromethorphan), both intestinal/hepatic CYP 3A4 (midazolam) and P-glycoprotein (P-gp) (digoxin). At steady state, there was a significant induction of CYP 1A2 and a slight induction on CYP 2C9. Potent inhibition of CYP 2D6 and both hepatic and intestinal CYP 3A4 activities were observed. P-gp activity is significantly inhibited after the first dose, but there was a slight induction at steady state. Practical recommendations deriving from this study are displayed below.

Studies in human liver microsomes indicated tipranavir is an inhibitor of CYP 1A2, CYP 2C9, CYP 2C19 and CYP 2D6. The potential net effect of tipranavir with ritonavir on CYP 2D6 is inhibition, because ritonavir is also a CYP 2D6 inhibitor. The *in vivo* net effect of tipranavir with ritonavir on CYP 1A2, CYP 2C9 and CYP 2C19, indicates, through a preliminary study, an inducing potential of tipranavir with ritonavir on CYP1A2 and, to a lesser extent, on CYP2C9 and P-gp after several days of treatment. Data are not available to indicate whether tipranavir inhibits or induces glucuronosyl transferases.

In vitro studies show that tipranavir is a substrate and also an inhibitor of P-gp.

It is difficult to predict the net effect of Aptivus co-administered with low dose ritonavir on oral bioavailability and plasma concentrations of agents that are dual substrates of CYP3A and P-gp. The net effect will vary depending on the relative affinity of the co-administered substance for CYP3A and P-gp, and the extent of intestinal first-pass metabolism/efflux.

Co-administration of Aptivus and agents that induce CYP3A and/or P-gp may decrease tipranavir concentrations and reduce its therapeutic effect (see list and details of considered agents, below). Co-administration of Aptivus and medicinal products that inhibit P-gp may increase tipranavir plasma concentrations.

Known and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in the table below.

Interaction table

Interactions between Aptivus and co-administered medicinal products are listed in the table below (increase is indicated as "↑", decrease as "↓", no change as "↔",once daily as "QD", twice daily as "BID").

Unless otherwise stated, studies detailed below have been performed with the recommended dosage of Aptivus/r (i.e. 500/200 mg BID). However, some PK interaction studies were not performed with this recommended dosage. Nevertheless, the results of many of these interaction studies can be extrapolated to the recommended dosage since the doses used (eg. TPV/r 500/100 mg, TPV/r 750/200 mg) represented extremes of hepatic enzyme induction and inhibition and bracketed the recommended dosage of Aptivus/r.

Drugs by therapeutic area	Interaction Geometric mean change (%)	Recommendations concerning co-administration
Anti-infectives		
Antiretrovirals		
Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)		
Since there is no significant impact of nucleoside and nucleotide analogues on the P450 enzyme system no dosage adjustment of Aptivus is required when co-administered with these agents.		
Abacavir 300 mg BID (TPV/r 750/100 mg BID)	Abacavir C_{max} ↓ 46% Abacavir AUC ↓ 36% The clinical relevance of this reduction has not been established, but may decrease the efficacy of abacavir. Mechanism unknown.	The concomitant use of Aptivus, co-administered with low dose ritonavir, with abacavir is not recommended unless there are no other available NRTIs suitable for patient management. In such cases no dosage adjustment of abacavir can be recommended (see section 4.4).
Didanosine 200 mg BID, ≥ 60 kg - 125 mg BID, < 60 kg (TPV/r 250/200 mg BID) (TPV/r 750/100 mg BID)	Didanosine C_{max} ↓ 43% Didanosine AUC ↓ 33% Didanosine C_{max} ↓ 24% Didanosine AUC ↔ The clinical relevance of this reduction in didanosine concentrations has not been established. Mechanism unknown.	Dosing of enteric-coated didanosine and Aptivus soft capsules, co-administered with low dose ritonavir, should be separated by at least 2 hours to avoid formulation incompatibility.
Emtricitabine No interaction study performed	Potential interactions with renal transporters cannot be fully excluded.	No dosage adjustment necessary in patients with normal renal function. In case of concomitant administration of emtricitabine and Aptivus/ritonavir, renal function should be evaluated before initiating the co-administration.
Lamivudine 150 mg BID (TPV/r 750/100 mg BID)	No clinically significant interaction is observed.	No dosage adjustment necessary.
Stavudine 40 mg BID ≥ 60 kg 30 mg BID < 60 kg (TPV/r 750/100 mg BID)	No clinically significant interaction is observed.	No dosage adjustment necessary.
Zidovudine 300 mg BID (TPV/r 750/100 mg BID)	Zidovudine C_{max} ↓ 49% Zidovudine AUC ↓ 36% The clinical relevance of this reduction has not been established, but may decrease the efficacy of zidovudine. Mechanism unknown.	The concomitant use of Aptivus, co-administered with low dose ritonavir with zidovudine is not recommended unless there are no other available NRTIs suitable for patient management. In such cases no dosage adjustment of zidovudine can be recommended (see section 4.4).
Tenofovir 300 mg QD (TPV/r 750/200 mg BID)	No clinically significant interaction is observed.	No dosage adjustment necessary.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz 600 mg QD	No clinically significant interaction is observed.	No dosage adjustment necessary.
Etravirine	Etravirine C_{max} ↓ 71% Etravirine AUC ↓ 76% Etravirine C_{min} ↓ 82% Concomitant use of Aptivus/ritonavir caused a decrease of etravirine exposure that could significantly impair the virologic response to etravirine.	Co-administration of etravirine and Aptivus/ritonavir is not recommended.
Nevirapine No interaction study performed	The limited data available from a phase IIa study in HIV-infected patients suggest that no significant interaction is expected between nevirapine and TPV/r. Moreover a study with TPV/r and another NNRTI (efavirenz) did not show any clinically relevant interaction (see above).	No dosage adjustment necessary.
Rilpivirine No interaction study performed	Concomitant use of rilpivirine with some ritonavir-boosted protease inhibitors has demonstrated an increase in the plasma concentrations of rilpivirine.	Close monitoring for signs of rilpivirine toxicity and possibly also dose adjustment of rilpivirine is recommended when co-administered with Aptivus/ritonavir.
Protease inhibitors (PIs)		
<u>According to current treatment guidelines, dual therapy with protease inhibitors is generally not recommended</u>		
Amprenavir/ritonavir 600/100 mg BID	Amprenavir C_{max} ↓ 39% Amprenavir AUC ↓ 44% Amprenavir C_{min} ↓ 55% The clinical relevance of this reduction in amprenavir concentrations has not been established. Mechanism unknown.	The concomitant use of Aptivus, co-administered with low dose ritonavir, with amprenavir/ritonavir is not recommended. If the combination is nevertheless considered necessary, a monitoring of the plasma levels of amprenavir is strongly encouraged (see section 4.4).
Atazanavir/ritonavir 300/100 mg QD (TPV/r 500/100 mg BID)	Atazanavir C_{max} ↓ 57% Atazanavir AUC ↓ 68% Atazanavir C_{min} ↓ 81% Mechanism unknown. Tipranavir C_{max} ↑ 8% Tipranavir AUC ↑ 20% Tipranavir C_{min} ↑ 75% Inhibition of CYP 3A4 by atazanavir/ritonavir and induction by tipranavir/r.	The concomitant use of Aptivus, co-administered with low dose ritonavir, with atazanavir/ritonavir is not recommended. If the co-administration is nevertheless considered necessary, a close monitoring of the safety of tipranavir and a monitoring of plasma concentrations of atazanavir are strongly encouraged (see section 4.4).
Lopinavir/ritonavir 400/100 mg BID	Lopinavir C_{max} ↓ 47% Lopinavir AUC ↓ 55% Lopinavir C_{min} ↓ 70%	The concomitant use of Aptivus, co-administered with low dose ritonavir, with lopinavir/ritonavir is not recommended.

	The clinical relevance of this reduction in lopinavir concentrations has not been established. Mechanism unknown.	If the combination is nevertheless considered necessary, a monitoring of the plasma levels of lopinavir is strongly encouraged (see section 4.4).
Saquinavir/ritonavir 600/100 mg QD	Saquinavir C_{max} ↓ 70% Saquinavir AUC ↓ 76% Saquinavir C_{min} ↓ 82% The clinical relevance of this reduction in saquinavir concentrations has not been established. Mechanism unknown.	The concomitant use of Aptivus, co-administered with low dose ritonavir, with saquinavir/ritonavir is not recommended. If the combination is nevertheless considered necessary, a monitoring of the plasma levels of saquinavir is strongly encouraged (see section 4.4).
Protease inhibitors other than those listed above	No data are currently available on interactions of tipranavir, co-administered with low dose ritonavir, with protease inhibitors other than those listed above.	Combination with Aptivus, co-administered with low dose ritonavir, is not recommended (see section 4.4)
Fusion inhibitors		
Enfuvirtide No interaction study performed	In studies where tipranavir co-administered with low-dose ritonavir was used with or without enfuvirtide, it has been observed that the steady-state plasma tipranavir trough concentration of patients receiving enfuvirtide were 45% higher as compared to patients not receiving enfuvirtide. No information is available for the parameters AUC and C_{max}. A pharmacokinetic interaction is mechanistically unexpected and the interaction has not been confirmed in a controlled interaction study.	The clinical impact of the observed data, especially regarding the tipranavir with ritonavir safety profile, remains unknown. Nevertheless, the clinical data available from the RESIST trials did not suggest any significant alteration of the tipranavir with ritonavir safety profile when combined with enfuvirtide as compared to patients treated with tipranavir with ritonavir without enfuvirtide.
Integrase strand transfer inhibitors		
Raltegravir 400 mg BID	Raltegravir C_{max} ↔ 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.
Pharmacokinetic enhancer		
Cobicistat and cobicistat-containing products	When co-administered, tipranavir and cobicistat exposures are markedly lower compared to that of tipranavir when boosted with low dose ritonavir.	Aptivus/ritonavir should not be administered concomitantly with cobicistat or cobicistat-containing products.

Anti-HCV agents		
Boceprevir No interaction study performed	In a pharmacokinetic study of healthy volunteers, boceprevir decreased the exposure of ritonavir, and some ritonavir-boosted protease inhibitors. Boceprevir exposure was reduced when co-administered with ritonavir-boosted lopinavir or ritonavir-boosted darunavir. These drug-drug interactions may reduce the effectiveness of HIV protease inhibitors and/or boceprevir when co-administered.	Coadministration of boceprevir with Aptivus/ritonavir is not recommended.
Telaprevir No interaction study performed	Telaprevir is metabolized in the liver by CYP3A and is a P-glycoprotein (P-gp) substrate, but other enzymes may be involved in the metabolism. When Aptivus/ritonavir is co-administered with telaprevir, a decrease or an increase of telaprevir exposure could be expected. There is a heterogeneous effect of telaprevir on ritonavir-boosted protease inhibitor drug plasma levels, depending on the protease inhibitors. Therefore, a modification of Aptivus exposure cannot be ruled out.	Coadministration of telaprevir with Aptivus/ritonavir is not recommended.
Antifungals		
Fluconazole 200 mg QD (Day 1) then 100 mg QD	Fluconazole ↔ Tipranavir C_{max} ↑ 32% Tipranavir AUC ↑ 50% Tipranavir C_{min} ↑ 69% Mechanism unknown	No dosage adjustments are recommended. Fluconazole doses >200 mg/day are not recommended.
Itraconazole **Ketoconazole** No interaction study performed	Based on theoretical considerations tipranavir, co-administered with low dose ritonavir, is expected to increase itraconazole or ketoconazole concentrations. Based on theoretical considerations, tipranavir or ritonavir concentrations might increase upon co-administration with itraconazole or ketoconazole.	Itraconazole or ketoconazole should be used with caution (doses >200 mg/day are not recommended).
Voriconazole No interaction study performed	Due to multiple CYP isoenzyme systems involved in voriconazole metabolism, it is difficult to predict the interaction with tipranavir, co-administered with low-dose ritonavir.	Based on the known interaction of voriconazole with low dose ritonavir (see voriconazole SmPC) the co-administration of tipranavir/r and voriconazole should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.

Anti-gouts		
Colchicine No interaction study performed	Based on theoretical considerations, colchicine concentrations may increase upon co-administration with tipranavir and low dose ritonavir, due to tipranavir/ritonavir CYP3A and P-gp inhibition. However a decrease of colchicine concentrations cannot be excluded since both tipranavir and ritonavir exhibit inducing potential towards CYP3A and P-gp. Colchicine is a substrate of CYP3A4 and P-gp (an intestinal efflux transporter).	A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with Aptivus/ritonavir is required (see section 4.4). In patients with renal or hepatic impairment, co-administration of colchicine in patients on Aptivus/ritonavir is contraindicated (see section 4.3).
Antibiotics		
Clarithromycin 500 mg BID	Clarithromycin C_{max} ↔ Clarithromycin AUC ↑ 19% Clarithromycin C_{min} ↑ 68% 14-OH-clarithromycin C_{max} ↓ 97% 14-OH-clarithromycin AUC ↓ 97% 14-OH-clarithromycin C_{min} ↓ 95% Tipranavir C_{max} ↑ 40% Tipranavir AUC ↑ 66% Tipranavir C_{min} ↑ 100% CYP 3A4 inhibition by tipranavir/r and P-gp (an intestinal efflux transporter) inhibition by clarithromycin.	Whilst the changes in clarithromycin parameters are not considered clinically relevant, the reduction in the 14-OH metabolite AUC should be considered for the treatment of infections caused by *Haemophilus influenzae* in which the 14-OH metabolite is most active. The increase of tipranavir C_{min} may be clinically relevant. Patients using clarithromycin at doses higher than 500 mg twice daily should be carefully monitored for signs of toxicity of clarithromycin and tipranavir. For patients with renal impairment dose reduction of clarithromycin should be considered (see clarithromycin and ritonavir product information).
Rifabutin 150 mg QD	Rifabutin C_{max} ↑ 70% Rifabutin AUC ↑ 190% Rifabutin C_{min} ↑ 114% 25-O-desacetylrifabutin C_{max} ↑ 3.2 fold 25-O-desacetylrifabutin AUC ↑ 21 fold 25-O-desacetylrifabutin C_{min} ↑ 7.8 fold Inhibition of CYP 3A4 by tipranavir/r No clinically significant change is observed in tipranavir PK parameters.	Dosage reductions of rifabutin by at least 75% of the usual 300 mg/day are recommended (ie 150 mg on alternate days, or three times per week). Patients receiving rifabutin with Aptivus, co-administered with low dose ritonavir, should be closely monitored for emergence of adverse events associated with rifabutin therapy. Further dosage reduction may be necessary.
Rifampicin	Co-administration of protease inhibitors with rifampicin substantially decreases protease inhibitor concentrations. In the case	Concomitant use of Aptivus, co-administered with low dose ritonavir, and rifampicin is contraindicated (see section 4.3).

	of tipranavir co-administered with low dose ritonavir, concomitant use with rifampicin is expected to result in sub-optimal levels of tipranavir which may lead to loss of virologic response and possible resistance to tipranavir.	Alternate antimycobacterial agents such as rifabutin should be considered.
Antimalarial		
Halofantrine **Lumefantrine** No interaction study performed	Based on theoretical considerations, tipranavir, co-administered with low dose ritonavir, is expected to increase halofantrine and lumefantrine concentrations. Inhibition of CYP 3A4 by tipranavir/r	Due to their metabolic profile and inherent risk of inducing torsades de pointes, administration of halofantrine and lumefantrine with Aptivus, co-administered with low dose ritonavir, is not recommended (see section 4.4).
Anticonvulsants		
Carbamazepine 200 mg BID	Carbamazepine total* C_{max} ↑ 13% Carbamazepine total* AUC ↑ 16% Carbamazepine total* C_{min} ↑ 23% *Carbamazepine total = total of carbamazepine and epoxy-carbamazepine (both are pharmacologically active moieties). The increase in carbamazepine total PK parameters is not expected to have clinical consequences. Tipranavir C_{min} ↓ 61% (compared to historical data) The decrease in tipranavir concentrations may result in decreased effectiveness. Carbamazepine induces CYP3A4.	Carbamazepine should be used with caution in combination with Aptivus, co-administered with low dose ritonavir. Higher doses of carbamazepine (> 200 mg) may result in even larger decreases in tipranavir plasma concentrations (see section 4.4).
Phenobarbital **Phenytoin** No interaction study performed	Phenobarbital and phenytoin induce CYP3A4.	Phenobarbital and phenytoin should be used with caution in combination with Aptivus, co-administered with low dose ritonavir (see section 4.4).
Antispasmodic		
Tolterodine No interaction study performed	Based on theoretical considerations, tipranavir, co-administered with low dose ritonavir, is expected to increase tolterodine concentrations. Inhibition of CYP 3A4 and CYP 2D6 by tipranavir/r	Co-administration 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).
HMG CoA reductase inhibitors		
Atorvastatin 10 mg QD	Atorvastatin C_{max} ↑ 8.6 fold Atorvastatin AUC ↑ 9.4 fold Atorvastatin C_{min} ↑ 5.2 fold Tipranavir ↔ Inhibition of CYP 3A4 by tipranavir/r	Co-administration of atorvastatin and Aptivus, co-administered with low dose ritonavir, is not recommended. Other HMG-CoA reductase inhibitors should be considered such as pravastatin, fluvastatin or rosuvastatin (See also section 4.4 and rosuvastatin and pravastatin recommendations). In cases where co-administration is necessary, the dose of 10 mg atorvastatin daily should not be exceeded. It is recommended to start with the lowest dose and careful clinical monitoring is necessary (see section 4.4).
Rosuvastatin 10 mg QD	Rosuvastatin C_{max} ↑ 123% Rosuvastatin AUC ↑ 37% Rosuvastatin C_{min} ↑ 6% Tipranavir ↔ Mechanism unknown.	Co-administration of Aptivus, co-administered with low dose ritonavir, and rosuvastatin should be initiated with the lowest dose (5 mg/day) of rosuvastatin, titrated to treatment response, and accompanied with careful clinical monitoring for rosuvastatin associated symptoms as described in the label of rosuvastatin.
Pravastatin No interaction study performed	Based on similarities in the elimination between pravastatin and rosuvastatin, TPV/r could increase the plasma levels of pravastatin. Mechanism unknown.	Co-administration of Aptivus, co-administered with low dose ritonavir, and pravastatin should be initiated with the lowest dose (10 mg/day) of pravastatin, titrated to treatment response, and accompanied with careful clinical monitoring for pravastatin associated symptoms as described in the label of pravastatin.
Simvastatin **Lovastatin** No interaction study performed	The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A for metabolism.	The concomitant use of Aptivus, co-administered with low dose ritonavir, with simvastatin or lovastatin are contra-indicated due to an increased risk of myopathy, including rhabdomyolysis (see section 4.3).

HERBAL PRODUCTS		
St. John's wort (*Hypericum perforatum*) No interaction study performed	Plasma concentrations of tipranavir can be reduced by concomitant use of the herbal preparation St John's wort (*Hypericum perforatum*). This is due to induction of drug metabolising enzymes by St John's wort.	Herbal preparations containing St. John's wort must not be combined with Aptivus, co-administered with low dose ritonavir. Co-administration of Aptivus with ritonavir, with St. John's wort is expected to substantially decrease tipranavir and ritonavir concentrations and may result in sub-optimal levels of tipranavir and lead to loss of virologic response and possible resistance to tipranavir.
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.
Oral contraceptives / Oestrogens		
Ethinyl oestradiol 0.035 mg / **Norethindrone** 1.0 mg QD (TPV/r 750/200 mg BID)	Ethinyl oestradiol C_{max} ↓ 52% Ethinyl oestradiol AUC ↓ 43% Mechanism unknown Norethindrone C_{max} ↔ Norethindrone AUC ↑ 27% Tipranavir ↔	The concomitant administration with Aptivus, co-administered with low dose ritonavir, is not recommended. Alternative or additional contraceptive measures are to be used when oestrogen based oral contraceptives are co-administered with Aptivus and low dose ritonavir. Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency (see sections 4.4 and 4.6).
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).

		Co-administrationof Aptivus/ritonavir with sildenafil, when used to treat pulmonary arterial hypertension, is contraindicated.
Tadalafil 10 mg QD	Tadalafil first-dose C_{max} ↓ 22% Tadalafil first-dose AUC ↑ 133% CYP 3A4 inhibition and induction by tipranavir/r Tadalafil steady-state C_{max} ↓ 30% Tadalafil steady-state AUC ↔ No clinically significant change is observed in tipranavir PK parameters.	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 include visual disturbances, hypotension, prolonged erection, and syncope).
Narcotic analgesics		
Methadone 5 mg QD	Methadone C_{max} ↓ 55% Methadone AUC ↓ 53% Methadone C_{min} ↓ 50% R-methadone C_{max} ↓ 46% R-methadone AUC ↓ 48% S-methadone C_{max} ↓ 62% S-methadone AUC ↓ 63% Mechanism unknown	Patients should be monitored for opiate withdrawal syndrome. Dosage of methadone may need to be increased.
Meperidine No interaction study performed	Tipranavir, co-administered with low dose ritonavir, is expected to decrease meperidine concentrations and increase normeperidine metabolite concentrations.	Dosage increase and long-term use of meperidine with Aptivus, co-administered with low dose ritonavir, are not recommended due to the increased concentrations of the metabolite normeperidine which has both analgesic activity and CNS stimulant activity (e.g. seizures).
Buprenorphine/Naloxone	Buprenorphine ↔ Norbuprenorphine AUC ↓ 79% Norbuprenorphine C_{max} ↓ 80% Norbuprenorphine C_{min} ↓ 80%	Due to reduction in the levels of the active metabolite norbuprenorphine, co-administration of Aptivus, co-administered with low dose ritonavir, and buprenorphine/naloxone may result in decreased clinical efficacy of buprenorphine. Therefore, patients should be monitored for opiate withdrawal syndrome.
Immunosupressants		
Cyclosporin **Tacrolimus** **Sirolimus** No interaction study performed	Concentrations of cyclosporin, tacrolimus, or sirolimus cannot be predicted when co-administered with tipranavir co-administered with low dose ritonavir, due to conflicting effect of tipranavir, co-administered with low dose ritonavir, on CYP 3A and P-gp.	More frequent concentration monitoring of these medicinal products is recommended until blood levels have been stabilised.

Antithrombotics		
Warfarin 10 mg QD	First-dose tipranavir/r: S-warfarin C_{max} ↔ S-warfarin AUC ↑ 18% Steady-state tipranavir/r: S-warfarin C_{max} ↓ 17% S-warfarin AUC ↓ 12% Inhibition of CYP 2C9 with first-dose tipranavir/r, then induction of CYP 2C9 with steady-state tipranavir/r	Aptivus, co-administered with low dose ritonavir, when combined with warfarin may be associated with changes in INR (International Normalised Ratio) values, and may affect anticoagulation (thrombogenic effect) or increase the risk of bleeding. Close clinical and biological (INR measurement) monitoring is recommended when warfarin and tipranavir are combined.
Antacids		
aluminium- and magnesium-based antacid QD	Tipranavir C_{max} ↓ 25% Tipranavir AUC ↓ 27% Mechanism unknown	Dosing of Aptivus, co-administered with low dose ritonavir, with antacids should be separated by at least a two hours time interval.
Proton pump inhibitors (PPIs)		
Omeprazole 40 mg QD	Omeprazole C_{max} ↓ 73% Omeprazole AUC ↓ 70% Similar effects were observed for the S-enantiomer, esomeprazole. Induction of CYP 2C19 by tipranavir/r Tipranavir ↔	The combined use of Aptivus, co-administered with low dose ritonavir, with either omeprazole or esomeprazole is not recommended (see section 4.4). If unavoidable, upward dose adjustments for either omeprazole or esomeprazole may be considered based on clinical response to therapy. There are no data available indicating that omeprazole or esomeprazole dose adjustments will overcome the observed pharmacokinetic interaction. Recommendations for maximal doses of omeprazole or esomeprazole are found in the corresponding product information. No tipranavir with ritonavir dose adjustment is required.
Lansoprazole **Pantoprazole** **Rabeprazole** No interaction study performed	Based on the metabolic profiles of tipranavir/r and the proton pump inhibitors, an interaction can be expected. As a result of CYP3A4 inhibition and CYP2C19 induction by tipranavir/r, lansoprazole and pantoprazole plasma concentrations are difficult to predict. Rabeprazole plasma concentrations might decrease as a result of induction of CYP2C19 by tipranavir/r.	The combined use of Aptivus, co-administered with low dose ritonavir, with proton pump inhibitors is not recommended (see section 4.4). If the co-administration is judged unavoidable, this should be done under close clinical monitoring.
H2-receptor antagonists		
No interaction study performed	No data are available for H2-receptor antagonists in combination with tipranavir and low dose ritonavir.	An increase in gastric pH that may result from H2-receptor antagonist therapy is not expected to have an impact on tipranavir plasma concentrations.

Antiarrhythmics		
Amiodarone **Bepridil** **Quinidine** No interaction study performed	Based on theoretical considerations, tipranavir, co-administered with low dose ritonavir, is expected to increase amiodarone, bepridil and quinidine concentrations. Inhibition of CYP 3A4 by tipranavir/r	The concomitant use of Aptivus, co-administered with low dose ritonavir, with amiodarone, bepridil or quinidine is contraindicated due to potential serious and/or life threatening events (see section 4.3)
Flecainide **Propafenone** **Metoprolol** (given in heart failure) No interaction study performed	Based on theoretical considerations, tipranavir, co-administered with low dose ritonavir, is expected to increase flecainide, propafenone and metoprolol concentrations. Inhibition of CYP 2D6 by tipranavir/r	The concomitant use of Aptivus, co-administered with low dose ritonavir, with flecainide, propafenone or metoprolol is contraindicated (see section 4.3)
Antihistamines		
Astemizole **Terfenadine** No interaction study performed	Based on theoretical considerations, tipranavir, co-administered with low dose ritonavir, is expected to increase astemizole and terfenadine concentrations. Inhibition of CYP 3A4 by tipranavir/r	The concomitant use of Aptivus, co-administered with low dose ritonavir, with astemizole or terfenadine is contraindicated due to potential serious and/or life threatening events (see section 4.3)
Ergot derivatives		
Dihydroergotamine **Ergonovine** **Ergotamine** **Methylergonovine** No interaction study performed	Based on theoretical considerations, tipranavir, co-administered with low dose ritonavir, is expected to increase dihydroergotamine, ergonovine, ergotamine and methylergonovine concentrations. Inhibition of CYP 3A4 by tipranavir/r	The concomitant use of Aptivus, co-administered with low dose ritonavir, with dihydroergotamine, ergonovine, ergotamine or methylergonovine is contraindicated due to potential serious and/or life threatening events (see section 4.3)
Gastrointestinal motility agents		
Cisapride No interaction study performed	Based on theoretical considerations, tipranavir, co-administered with low dose ritonavir, is expected to increase cisapride concentrations. Inhibition of CYP 3A4 by tipranavir/r	The concomitant use of Aptivus, co-administered with low dose ritonavir, with cisapride is contraindicated due to potential serious and/or life threatening events (see section 4.3)
Antipsychotics		
Pimozide **Sertindole** **Quetiapine** No interaction study performed	Based on theoretical considerations, tipranavir, co-administered with low dose ritonavir, is expected to increase pimozide, sertindole and quetiapine concentrations. Inhibition of CYP 3A4 by tipranavir/r	The concomitant use of Aptivus, co-administered with low dose ritonavir, with pimozide, sertindole, or quetiapine is contraindicated due to potential serious and/or life threatening events, including coma (see section 4.3)

Sedatives/hypnotics		
Midazolam 2 mg QD (iv) **Midazolam** 5 mg QD (po)	First-dose tipranavir/r: Midazolam C_{max} ↔ Midazolam AUC ↑ 5.1 fold Steady-state tipranavir/r: Midazolam C_{max} ↓ 13% Midazolam AUC ↑ 181% First-dose tipranavir/r Midazolam C_{max} ↑ 5.0 fold Midazolam AUC ↑ 27 fold Steady-state tipranavir/r Midazolam C_{max} ↑ 3.7 fold Midazolam AUC ↑ 9.8 fold Ritonavir is a potent inhibitor of CYP3A4 and therefore affect drugs metabolised by this enzyme.	Concomitant use of Aptivus, co-administered with low dose ritonavir, and oral midazolam is contra-indicated (see section 4.3). If Aptivus with ritonavir is administered with parenteral midazolam, close clinical monitoring for respiratory depression and/or prolonged sedation should be instituted and dosage adjustment should be considered.
Triazolam No interaction study performed	Based on theoretical considerations, tipranavir, co-administered with low dose ritonavir, is expected to increase triazolam concentrations. Inhibition of CYP 3A4 by tipranavir/r	The concomitant use of Aptivus, co-administered with low dose ritonavir, with triazolam is contraindicated due to potential serious and/or life threatening events (see section 4.3)
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.
Others		
Theophylline No interaction study performed	Based on data from the cocktail study where caffeine (CYP1A2 substrate) AUC was reduced by 43%, tipranavir with ritonavir is expected to decrease theophylline concentrations. Induction of CYP 1A2 by tipranavir/r	Theophylline plasma concentrations should be monitored during the first two weeks of co-administration with Aptivus, co-administered with low dose ritonavir, and the theophylline dose should be increased as needed.
Desipramine No interaction study performed	tipranavir, co-administered with low dose ritonavir, is expected to increase desipramine concentrations	Dosage reduction and concentration monitoring of desipramine is recommended.

	Inhibition of CYP 2D6 by tipranavir/r	
Digoxin 0.25 mg QD iv **Digoxin** 0.25 mg QD po	First-dose tipranavir/r Digoxin C_{max} ↔ Digoxin AUC ↔ Steady-state tipranavir/r Digoxin C_{max} ↓ 20% Digoxin AUC ↔ First-dose tipranavir/r Digoxin C_{max} ↑ 93% Digoxin AUC ↑ 91% Transient inhibition of P-gp by tipranavir/r, followed by induction of P-gp by tipranavir/r at steady-state Steady-state tipranavir/r Digoxin C_{max} ↓ 38% Digoxin AUC ↔	Monitoring of digoxin serum concentrations is recommended until steady state has been obtained.
Trazodone Interaction study performed only with ritonavir	In a pharmacokinetic study performed in healthy volunteers, concomitant use of low dose ritonavir (200 mg twice daily) with a single dose of trazodone led to an increased plasma concentration of trazodone (AUC increased by 2.4 fold). Adverse events of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir in this study. However, it is unknown whether the combination of tipranavir with ritonavir might cause a larger increase in trazodone exposure.	The combination should be used with caution and a lower dose of trazodone should be considered.
Bupropion 150 mg BID	Bupropion C_{max} ↓ 51% Bupropion AUC ↓ 56% Tipranavir ↔ The reduction of bupropion plasma levels is likely due to induction of CYP2B6 and UGT activity by RTV	If the co-administration with bupropion is judged unavoidable, this should be done under close clinical monitoring for bupropion efficacy, without exceeding the recommended dosage, despite the observed induction.
Loperamide 16 mg QD	Loperamide C_{max} ↓ 61% Loperamide AUC ↓ 51% Mechanism unknown Tipranavir C_{max} ↔ Tipranavir AUC ↔ Tipranavir C_{min} ↓ 26%	A pharmacodynamic interaction study in healthy volunteers demonstrated that administration of loperamide and Aptivus, co-administered with low dose ritonavir, does not cause any clinically relevant change in the respiratory response to carbon dioxide. The clinical relevance of the reduced loperamide plasma

		concentration is unknown.
Fluticasone propionate Interaction study performed only with ritonavir	In a clinical study where ritonavir 100 mg capsules bid were co-administered with 50 µg intranasal fluticasone propionate (4 times daily) for 7 days in healthy subjects, the fluticasone propionate plasma levels increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86% (90% confidence interval 82-89%). Greater effects may be expected when fluticasone propionate is inhaled. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate; this could also occur with other corticosteroids metabolised via the P450 3A pathway e.g. budesonide. It is unknown whether the combination of tipranavir with ritonavir might cause a larger increase in fluticasone exposure.	Concomitant administration of Aptivus, co-administered with low dose ritonavir, and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4). A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g. beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may have to be performed over a longer period. The effects of high fluticasone systemic exposure on ritonavir plasma levels are as yet unknown.

4.6 Fertility, pregnancy and lactation

Contraception in males and females
Tipranavir adversely interacts with oral contraceptives. Therefore, an alternative, effective, safe method of contraception should be used during treatment (see section 4.5).

Pregnancy
There are no adequate data from the use of tipranavir in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Tipranavir should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breastfeeding
Consistent with the recommendation that HIV-infected mothers should not breast-feed their infants under any circumstances to avoid risking postnatal transmission of HIV, mothers should discontinue breast-feeding if they are receiving Aptivus.

Fertility
Clinical data on fertility are not available for tipranavir. Preclinical studies performed with tipranavir showed no adverse effect on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Dizziness, somnolence, and fatigue have been reported in some patients; therefore, caution should be recommended when driving a car or operating machinery. If patients experience fatigue, dizziness, or somnolence they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile
Amongst the most common adverse reactions reported for Aptivus were gastrointestinal complaints such as diarrhoea and nausea as well as hyperlipidaemia. The most serious adverse reactions include hepatic impairment and liver toxicity. Intracranial haemorrhage (ICH) was only observed in post marketing experience (see section 4.4).

Aptivus co-administered with low dose ritonavir, has been associated with reports of significant liver toxicity. In Phase III RESIST trials, the frequency of transaminase elevations was significantly increased in the tipranavir with ritonavir arm compared to the comparator arm. Close monitoring is therefore needed in patients treated with Aptivus, co-administered with low dose ritonavir (see section 4.4).

Limited data are currently available for the use of Aptivus, co-administered with low dose ritonavir, in patients co-infected with hepatitis B or C. Aptivus should therefore be used with caution in patients co-infected with hepatitis B or C. Aptivus should be used in this patient population only if the potential benefit outweighs the potential risk, and with increased clinical and laboratory monitoring.

Tabulated summary of adverse reactions
Assessment of adverse reactions from HIV-1 clinical study data is based on experience in all Phase II and III trials in adults treated with the 500 mg tipranavir with 200 mg ritonavir dose twice daily (n=1397) and are listed below by system organ class and frequency according to the following categories:
Very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000)

Tabulated summary of adverse reactions associated with Aptivus based on clinical studies and post-marketing experience:

Blood and lymphatic system disorders	
uncommon	neutropenia, anaemia, thrombocytopenia
Immune system disorders	
uncommon	hypersensitivity
Metabolism and nutrition disorders	
common	hypertriglyceridaemia, hyperlipidaemia
uncommon	anorexia, decreased appetite, weight decreased, hyperamylasaemia, hypercholesterolaemia, diabetes mellitus, hyperglycaemia
rare	dehydration, facial wasting
Psychiatric disorders	
uncommon	insomnia, sleep disorder
Nervous system disorders	
common	headache
uncommon	dizziness, neuropathy peripheral, somnolence
rare	intracranial haemorrhage*
Respiratory, thoracic and mediastinal disorders	
uncommon	dyspnoea

Gastrointestinal disorders	
very common	diarrhoea, nausea
common	vomiting, flatulence, abdominal pain, abdominal distension, dyspepsia
uncommon	gastrooesophageal reflux disease, pancreatitis
rare	lipase increased
Hepatobiliary disorders	
uncommon	hepatic enzyme increased (ALAT, ASAT), cytolytic hepatitis, liver function test abnormal (ALAT, ASAT), hepatitis toxic
rare	hepatic failure (including fatal outcome), hepatitis, hepatic steatosis, hyperbilirubinaemia
Skin and subcutaneous tissue disorders	
common	rash
uncommon	pruritus, lipohypertrophy, exanthem, lipoatrophy, lipodystrophy acquired
Musculoskeletal and connective tissue disorders	
uncommon	myalgia, muscle spasms
Renal and urinary disorders	
uncommon	renal failure
General disorders and administration site conditions	
common	fatigue
uncommon	pyrexia, influenza like illness, malaise

***** see section Description of selected adverse reactions "Bleeding" for source of information

Description of selected adverse reactions

The following clinical safety features (hepatotoxicity, hyperlipidaemia, bleeding events, rash) were seen at higher frequency among tipranavir with ritonavir treated patients when compared with the comparator arm treated patients in the RESIST trials, or have been observed with tipranavir with ritonavir administration. The clinical significance of these observations has not been fully explored.

Hepatotoxicity

After 48 weeks of follow-up, the frequency of Grade 3 or 4 ALAT and/or ASAT abnormalities was higher in tipranavir with ritonavir patients compared with comparator arm patients (10% and 3.4%, respectively). Multivariate analyses showed that baseline ALAT or ASAT above DAIDS Grade 1 and co-infection with hepatitis B or C were risk factors for these elevations. Most patients were able to continue treatment with tipranavir with ritonavir.

Hyperlipidaemia

Grade 3 or 4 elevations of triglycerides occurred more frequently in the tipranavir with ritonavir arm compared with the comparator arm. At 48 weeks these rates were 25.2% of patients in the tipranavir with ritonavir arm and 15.6% in the comparator arm.

Bleeding

This adverse reaction was identified through post-marketing surveillance but not observed in randomised controlled clinical trials (n=6300).

RESIST participants receiving tipranavir with ritonavir tended to have an increased risk of bleeding; at 24 weeks the relative risk was 1.98 (95% CI=1.03, 3.80). At 48-weeks the relative risk decreased to 1.27 (95% CI=0.76, 2.12). There was no pattern for the bleeding events and no difference between treatment groups in coagulation parameters. The significance of this finding is being further monitored.
Fatal and non-fatal intracranial haemorrhage (ICH) have been reported in patients receiving tipranavir, many of whom had other medical conditions or were receiving concomitant medicinal products that may have caused or contributed to these events. However, in some cases the role of tipranavir cannot be excluded. No pattern of abnormal haematological or coagulation parameters has been observed in patients in general, or preceding the development of ICH. Therefore, routine measurement of coagulation parameters is not currently indicated in the management of patients on Aptivus.
An increased risk of ICH has previously been observed in patients with advanced HIV disease/AIDS such as those treated in the Aptivus clinical trials.

Rash
An interaction study in women between tipranavir, co-administered with low dose ritonavir, and ethinyl oestradiol/norethindrone demonstrated a high frequency of non-serious rash. In the RESIST trials, the risk of rash was similar between tipranavir with ritonavir and comparator arms (16.3% vs. 12.5%, respectively; see section 4.4). No cases of Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis have been reported in the clinical development programme of tipranavir.

Laboratory abnormalities
Frequencies of marked clinical laboratory abnormalities (Grade 3 or 4) reported in at least 2% of patients in the tipranavir with ritonavir arms in the phase III clinical studies (RESIST-1 and RESIST-2) after 48-weeks were increased ASAT (6.1%), increased ALAT (9.7%), increased amylase (6.0%), increased cholesterol (4.2%), increased triglycerides (24.9%), and decreased white blood cell count (5.7%).

Combination antiretroviral therapy, including regimens containing a protease inhibitor, is associated with redistribution of body fat in some patients, including loss of peripheral subcutaneous fat, increased intra-abdominal fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump). Protease inhibitors are also associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance and hyperglycaemia.

Increased CPK, myalgia, myositis and, rarely, rhabdomyolysis, have been reported with protease inhibitors, particularly in combination with nucleoside reverse transcriptase inhibitors.

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

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

<u>Paediatric population</u>
In an open-label, dose-finding study of tipranavir plus ritonavir (Trial 1182.14), 28 children who were 12 years of age or above received Aptivus capsules. In general, adverse reactions were similar to those seen in adults, with the exception of vomiting, rash and pyrexia, which were reported more frequently in children than in adults. The most frequently reported moderate or severe adverse reactions in the 48 week analyses are noted below.

Most frequently reported moderate or severe adverse reactions in paediatric patients aged 12 to 18 years who took Aptivus capsules (reported in 2 or more children, Trial 1182.14, week 48 analyses, Full Analysis Set).

Total patients treated (N)	**28**
Events [N(%)]	
Vomiting/ retching	3 (10.7)
Nausea	2 (7.1)
Abdominal pain[1]	2 (7.1)
Rash[2]	3 (10.7)
Insomnia	2 (7.1)
ALAT increased	4 (14.3)

[1] Includes abdominal pain (N=1) and dyspepsia (N=1).

[2] Rash consists of one or more of the preferred terms of rash, drug eruption, rash macular, rash papular, erythema, rash maculo-papular, rash pruritic, and urticaria

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Human experience with tipranavir overdose is very limited. No specific signs and symptoms of overdose are known. Generally, an increased frequency and higher severity of adverse reactions may result from overdose.

There is no known antidote for tipranavir overdose. Treatment of overdose should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. If indicated, elimination of unabsorbed tipranavir should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed substance. Since tipranavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, protease inhibitors, ATC code: J05AE09

Mechanism of action

The human immunodeficiency virus (HIV-1) encodes an aspartyl protease that is essential for the cleavage and maturation of viral protein precursors. Tipranavir is a non-peptidic inhibitor of the HIV-1 protease that inhibits viral replication by preventing the maturation of viral particles.

Antiviral activity *in vitro*

Tipranavir inhibits the replication of laboratory strains of HIV-1 and clinical isolates in acute models of T-cell infection, with 50% and 90% effective concentrations (EC_{50} and EC_{90}) ranging from 0.03 to 0.07 µM (18-42 ng/ml) and 0.07 to 0.18 µM (42-108 ng/ml), respectively. Tipranavir demonstrates antiviral activity *in vitro* against a broad panel of HIV-1 group M non-clade B isolates (A, C, D, F, G, H, CRF01 AE, CRF02 AG, CRF12 BF). Group O and HIV-2 isolates have reduced susceptibility *in vitro* to tipranavir with EC_{50} values ranging from 0.164-1 µM and 0.233-0.522 µM, respectively. Protein binding studies have shown that the antiviral activity of tipranavir decreases on average 3.75-fold in conditions where human serum is present.

Resistance
The development of resistance to tipranavir *in vitro* is slow and complex. In one particular *in vitro* resistance experiment, an HIV-1 isolate that was 87-fold resistant to tipranavir was selected after 9 months, and contained 10 mutations in the protease: L10F, I13V, V32I, L33F, M36I, K45I, I54V/T, A71V, V82L, I84V as well as a mutation in the gag polyprotein CA/P2 cleavage site. Reverse genetic experiments showed that the presence of 6 mutations in the protease (I13V, V32I, L33F, K45I, V82L, I84V) was required to confer > 10-fold resistance to tipranavir while the full 10-mutation genotype conferred 69-fold resistance to tipranavir. *In vitro*, there is an inverse correlation between the degree of resistance to tipranavir and the capacity of viruses to replicate. Recombinant viruses showing ≥ 3-fold resistance to tipranavir grow at less than 1% of the rate detected for wild type HIV-1 in the same conditions. Tipranavir resistant viruses which emerge *in vitro* from wild-type HIV-1 show decreased susceptibility to the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir and ritonavir but remain sensitive to saquinavir.

Through a series of multiple stepwise regression analyses of baseline and on-treatment genotypes from all clinical studies, 16 amino acids have been associated with reduced tipranavir susceptibility and/or reduced 48-week viral load response: 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D and 84V. Clinical isolates that exhibited a ≥ 10-fold decrease in tipranavir susceptibility harboured 8 or more tipranavir-associated mutations. In Phase II and III clinical trials, 276 patients with on-treatment genotypes have demonstrated that the predominant emerging mutations with tipranavir treatment are L33F/I/V, V82T/L and I84V. Combination of all three of these is usually required for reduced susceptibility. Mutations at position 82 occur via two pathways: one from pre-existing mutation 82A selecting to 82T, the other from wild type 82V selecting to 82L.

Cross-resistance
Tipranavir maintains significant antiviral activity (< 4-fold resistance) against the majority of HIV-1 clinical isolates showing post-treatment decreased susceptibility to the currently approved protease inhibitors: amprenavir, atazanavir, indinavir, lopinavir, ritonavir, nelfinavir and saquinavir. Greater than 10-fold resistance to tipranavir is uncommon (< 2.5% of tested isolates) in viruses obtained from highly treatment experienced patients who have received multiple peptidic protease inhibitors.

ECG evaluation
The effect of tipranavir with low dose of ritonavir on the QTcF interval was measured in a study in which 81 healthy subjects received 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.

Clinical pharmacodynamic data
This indication is based on the results of two phase III studies, performed in highly pre-treated adult patients (median number of 12 prior antiretroviral agents) with virus resistant to protease inhibitors and of one phase II study investigating pharmacokinetics, safety and efficacy of Aptivus in mostly treatment-experienced adolescent patients aged 12 to 18 years.

The following clinical data is derived from analyses of 48-week data from ongoing studies (RESIST-1 and RESIST-2) measuring effects on plasma HIV RNA levels and CD4 cell counts. RESIST-1 and RESIST-2 are ongoing, randomised, open-label, multicentre studies in HIV-positive, triple-class experienced patients, evaluating treatment with 500 mg tipranavir co-administered with low dose ritonavir (200 mg; twice daily) plus an optimised background regimen (OBR) individually defined for each patient based on genotypic resistance testing and patient history. The comparator regimen included a ritonavir-boosted PI (also individually defined) plus an OBR. The ritonavir-boosted PI was chosen from among saquinavir, amprenavir, indinavir or lopinavir/ritonavir.

All patients had received at least two PI-based antiretroviral regimens and were failing a PI-based regimen at the time of study entry. At least one primary protease gene mutation from among 30N, 46I,

46L, 48V, 50V, 82A, 82F, 82L, 82T, 84V or 90M had to be present at baseline, with not more than two mutations on codons 33, 82, 84 or 90.

After Week 8, patients in the comparator arm who met the protocol defined criteria of initial lack of virologic response had the option of discontinuing treatment and switching over to tipranavir with ritonavir in a separate roll-over study.

The 1483 patients included in the primary analysis had a median age of 43 years (range 17-80), were 86% male, 75% white, 13% black and 1% Asian. In the tipranavir and comparator arms median baseline CD4 cell counts were 158 and 166 cells/mm^3, respectively, (ranges 1-1893 and 1-1184 cells/mm^3); median baseline plasma HIV-1 RNA was 4.79 and 4.80 log_{10} copies/ml, respectively (ranges 2.34-6.52 and 2.01-6.76 log_{10} copies/ml).

Patients had prior exposure to a median of 6 NRTIs, 1 NNRTI, and 4 PIs. In both studies, a total of 67% patient viruses were resistant and 22% were possibly resistant to the pre-selected comparator PIs. A total of 10% of patients had previously used enfuvirtide. Patients had baseline HIV-1 isolates with a median of 16 HIV-1 protease gene mutations, including a median of 3 primary protease gene mutations D30N, L33F/I, V46I/L, G48V, I50V, V82A/F/T/L, I84V, and L90M. With respect to mutations on codons 33, 82, 84 and 90 approximately 4% had no mutations, 24% had mutations at codons 82 (less than 1% of patients had the mutation V82L) and 90, 18% had mutations at codons 84 and 90 and 53% had at least one key mutation at codon 90. One patient in the tipranavir arm had four mutations. In addition the majority of participants had mutations associated with both NRTI and NNRTI resistance. Baseline phenotypic susceptibility was evaluated in 454 baseline patient samples. There was an average decrease in susceptibility of 2-fold wild type (WT) for tipranavir, 12-fold WT for amprenavir, 55-fold WT for atazanavir, 41-fold WT for indinavir, 87-fold WT for lopinavir, 41-fold WT for nelfinavir, 195-fold WT for ritonavir, and 20-fold WT for saquinavir.

Combined 48-week treatment response (composite endpoint defined as patients with a confirmed ≥1 log RNA drop from baseline and without evidence of treatment failure) for both studies was 34% in the tipranavir with ritonavir arm and 15% in the comparator arm. Treatment response is presented for the overall population (displayed by enfuvirtide use), and detailed by PI strata for the subgroup of patients with genotypically resistant strains in the Table below.

Treatment response* at week 48 (pooled studies RESIST-1 and RESIST-2 in treatment-experienced patients)

RESIST study	Tipranavir/**RTV**		**CPI/RTV****		**p-value**
	n (%)	**N**	**n (%)**	**N**	
Overall population					
FAS	255 (34.2)	746	114 (15.5)	737	<0.0001
PP	171 (37.7)	454	74 (17.1)	432	<0.0001
- with ENF (FAS)	85 (50.0)	170	28 (20.7)	135	<0.0001
- without ENF (FAS)	170 (29.5)	576	86 (14.3)	602	<0.0001
Genotypically Resistant					
LPV/rtv					
FAS	66 (28.9)	228	23 (9.5)	242	<0.0001
PP	47 (32.2)	146	13 (9.1)	143	<0.0001
APV/rtv					
FAS	50 (33.3)	150	22 (14.9)	148	<0.0001
PP	38 (39.2)	97	17 (18.3)	93	0.0010
SQV/rtv					
FAS	22 (30.6)	72	5 (7.0)	71	<0.0001
PP	11 (28.2)	39	2 (5.7)	35	0.0650
IDV/rtv					
FAS	6 (46.2)	13	1 (5.3)	19	0.0026
PP	3 (50.0)	6	1 (7.1)	14	0.0650

* Composite endpoint defined as patients with a confirmed 1 log RNA drop from baseline and without evidence of treatment failure
** Comparator PI/RTV: LPV/r 400 mg/100 mg twice daily (n=358), IDV/r 800 mg/100 mg twice daily (n=23), SQV/r 1000 mg/100 mg twice daily or 800 mg/200 mg twice daily (n=162), APV/r 600 mg/100 mg twice daily (n=194)
ENF Enfuvirtide; FAS Full Analysis Set; PP Per Protocol; APV/rtv Amprenavir/ritonavir; IDV/rtv Indinavir/ritonavir; LPV/rtv Lopinavir/ritonavir; SQV/rtv Saquinavir/ritonavir

Combined 48-week median time to treatment failure for both studies was 115 days in the tipranavir with ritonavir arm and 0 days in the comparator arm (no treatment response was imputed to day 0).

Through 48 weeks of treatment, the proportion of patients in the tipranavir with ritonavir arm compared to the comparator PI/ritonavir arm with HIV-1 RNA < 400 copies/ml was 30% and 14% respectively, and with HIV-1 RNA < 50 copies/ml was 23% and 10% respectively. Among all randomised and treated patients, the median change from baseline in HIV-1 RNA at the last measurement up to Week 48 was -0.64 $\log_{10}$ copies/ml in patients receiving tipranavir with ritonavir versus -0.22 $\log_{10}$ copies/ml in the comparator PI/ritonavir arm.

Among all randomised and treated patients, the median change from baseline in CD4+ cell count at the last measurement up to Week 48 was +23 cells/mm^3 in patients receiving tipranavir with ritonavir (N=740) versus +4 cells/mm^3 in the comparator PI/ritonavir (N=727) arm.

The superiority of tipranavir co-administered with low dose ritonavir over the comparator protease inhibitor/ritonavir arm was observed for all efficacy parameters at week 48. It has not been shown that tipranavir is superior to these boosted comparator protease inhibitors in patients harbouring strains susceptible to these protease inhibitors. RESIST data also demonstrate that tipranavir co-administered with low dose ritonavir exhibits a better treatment response at 48 weeks when the OBR contains genotypically available antiretroviral agents (e.g. enfuvirtide).

At present there are no results from controlled trials evaluating the effect of tipranavir on clinical progression of HIV.

Paediatric population
HIV-positive, paediatric patients, aged 2 through 18 years, were studied in a randomized, open-label, multicenter study (trial 1182.14). Patients were required to have a baseline HIV-1 RNA concentration of at least 1500 copies/ml, were stratified by age (2 to < 6 years, 6 to < 12 years and 12 to 18 years) and randomized to receive one of two tipranavir with ritonavir dose regimens: 375 mg/m^2/150 mg/m^2 dose, compared to the 290 mg/m^2/115 mg/m^2 dose, plus background therapy of at least two non-protease inhibitor antiretroviral medicinal products, optimized using baseline genotypic resistance testing. All patients initially received Aptivus oral solution. Paediatric patients who were 12 years or older and received the maximum dose of 500 mg/200 mg twice daily could change to Aptivus capsules from study day 28. The trial evaluated pharmacokinetics, safety and tolerability, as well as virologic and immunologic responses through 48 weeks.

No data are available on the efficacy and safety of Aptivus capsules in children less than 12 years of age. Since Aptivus capsules and oral solution are not bioequivalent, results obtained with the oral solution cannot be extrapolated to the capsules (see also section 5.2). In patients with a body surface area of less than 1.33 m^2 appropriate dose adjustments cannot be achieved with the capsule formulation.

The baseline characteristics and the key efficacy results at 48 weeks for the paediatric patients receiving Aptivus capsules are displayed in the tables below. Data on the 29 patients who switched to capsules during the first 48 weeks are presented. Due to limitations in the study design (e.g. non-randomized switch allowed according to patient/clinician decision), any comparisons between patients taking capsules and oral solution are not meaningful.

Baseline characteristics for patients 12 – 18 years of age who took capsule

Variable		Value
Number of Patients		29
Age-Median (years)		15.1
Gender	% Male	48.3%
Race	% White	69.0%
	% Black	31.0%
	% Asian	0.0%
Baseline HIV-1 RNA (log_{10} copies/ml)	Median (Min – Max)	4.6 (3.0 – 6.8)
	% with VL > 100,000 copies/ml	27.6%
Baseline CD4+ (cells/mm^3)	Median (Min – Max)	330 (12 – 593)
	% ≤ 200	27.6%
Baseline % CD4+ cells	Median (Min – Max)	18.5% (3.1% – 37.4%)
Previous ADI*	% with Category C	29.2%
Treatment history	% with any ARV	96.6%
	Median # previous NRTIs	5
	Median # previous NNRTIs	1
	Median # previous PIs	3

* AIDS defining illness

Key efficacy results at 48 weeks for patients 12 – 18 years of age who took capsule

Endpoint	Result
Number of patients	29
Primary efficacy endpoint: % with VL < 400	31.0%
Median change from baseline in log10 HIV-1 RNA (copies/ml)	-0.79
Median change from baseline in CD4+ cell count (cells/mm3)	39
Median change from baseline in % CD4+ cells	3%

Analyses of tipranavir resistance in treatment experienced patients

Tipranavir with ritonavir response rates in the RESIST studies were assessed by baseline tipranavir genotype and phenotype. Relationships between baseline phenotypic susceptibility to tipranavir, primary PI mutations, protease mutations at codons 33, 82, 84 and 90, tipranavir resistance-associated mutations, and response to tipranavir with ritonavir therapy were assessed.

Of note, patients in the RESIST studies had a specific mutational pattern at baseline of at least one primary protease gene mutation among codons 30N, 46I, 46L, 48V, 50V, 82A, 82F, 82L, 82T, 84V or 90M, and no more than two mutations on codons 33, 82, 84 or 90.

The following observations were made:

– *Primary PI mutations*

Analyses were conducted to assess virological outcome by the number of primary PI mutations (any change at protease codons 30, 32, 36, 46, 47, 48, 50, 53, 54, 82, 84, 88 and 90) present at baseline. Response rates were higher in tipranavir with ritonavir patients than comparator PI boosted with ritonavir in new enfuvirtide patients, or patients without new enfuvirtide. However, without new enfuvirtide some patients began to lose antiviral activity between weeks 4 and 8.

– *Mutations at protease codons 33, 82, 84 and 90*

A reduced virological response was observed in patients with viral strains harbouring two or more mutations at HIV protease codons 33, 82, 84 or 90, and not receiving new enfuvirtide.

– *Tipranavir resistance-associated mutations*

Virological response to tipranavir with ritonavir therapy has been evaluated using a tipranavir-associated mutation score based on baseline genotype in RESIST-1 and RESIST-2 patients. This score (counting the 16 amino acids that have been associated with reduced tipranavir susceptibility and/or reduced viral load response: 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D and 84V) was applied to baseline viral protease sequences. A correlation between the tipranavir mutation score and response to tipranavir with ritonavir therapy at week 48 has been established.

This score has been determined from the selected RESIST patient population having specific mutation inclusion criteria and therefore extrapolation to a wider population mandates caution.

At 48-weeks, a higher proportion of patients receiving tipranavir with ritonavir achieved a treatment response in comparison to the comparator protease inhibitor/ritonavir for nearly all of the possible combinations of genotypic resistance mutations (see table below).

Proportion of patients achieving treatment response at Week 48 (confirmed ≥1 $\log_{10}$ copies/ml decrease in viral load compared to baseline), according to tipranavir baseline mutation score and enfuvirtide use in RESIST patients

	New ENF	No New ENF*
Number of TPV Score Mutations**	TPV/r	TPV/r
0,1	73%	53%
2	61%	33%
3	75%	27%
4	59%	23%
≥ 5	47%	13%
All patients	61%	29%

* Includes patients who did not receive ENF and those who were previously treated with and continued ENF

**Mutations in HIV protease at positions L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, 58E, H69K, T74P, V82L/T, N83D or I84V

ENF Enfuvirtide; TPV/r Tipranavir with ritonavir

Sustained HIV-1 RNA decreases up to week 48 were mainly observed in patients who received tipranavir with ritonavir and new enfuvirtide. If patients did not receive tipranavir with ritonavir with new enfuvirtide, diminished treatment responses at week 48 were observed, relative to new enfuvirtide use (see Table below).

Mean decrease in viral load from baseline to week 48, according to tipranavir baseline mutation score and enfuvirtide use in RESIST patients

	New ENF	No New ENF*
Number of TPV Score Mutations**	TPV/r	TPV/r
0, 1	-2.3	-1.6
2	-2.1	-1.1
3	-2.4	-0.9
4	-1.7	-0.8
≥ 5	-1.9	-0.6
All patients	-2.0	-1.0

* Includes patients who did not receive ENF and those who were previously treated with and continued ENF
** Mutations in HIV protease at positions L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, 58E, H69K, T74P, V82L/T, N83D or I84V
ENF Enfuvirtide; TPV/r Tipranavir with ritonavir

– *Tipranavir phenotypic resistance*
Increasing baseline phenotypic fold change to tipranavir in isolates is correlated to decreasing virological response. Isolates with baseline fold change of >0 to 3 are considered susceptible; isolates with >3 to 10 fold changes have decreased susceptibility; isolates with >10 fold changes are resistant.

Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change with additional data, and it is recommended to always consult current interpretation systems for analysing resistance test results.

5.2 Pharmacokinetic properties

In order to achieve effective tipranavir plasma concentrations and a twice daily dosing regimen, coadministration of tipranavir with low dose ritonavir twice daily is essential (see section 4.2). Ritonavir acts by inhibiting hepatic cytochrome P450 CYP3A, the intestinal P-glycoprotein (P-gp) efflux pump and possibly intestinal cytochrome P450 CYP3A as well. As demonstrated in a dose-ranging evaluation in 113 HIV-negative healthy male and female volunteers, ritonavir increases AUC_{0-12h}, C_{max} and C_{min} and decreases the clearance of tipranavir. 500 mg Tipranavir co-administered with low dose ritonavir (200 mg; twice daily) was associated with a 29-fold increase in the geometric mean morning steady-state trough plasma concentrations compared to tipranavir 500 mg twice daily without ritonavir.

Absorption
Absorption of tipranavir in humans is limited, though no absolute quantification of absorption is available. Tipranavir is a P-gp substrate, a weak P-gp inhibitor and appears to be a potent P-gp inducer as well. Data suggest that, although ritonavir is a P-gp inhibitor, the net effect of Aptivus, co-administered with low dose ritonavir, at the proposed dose regimen at steady-state, is P-gp induction. Peak plasma concentrations are reached within 1 to 5 hours after dose administration depending upon the dosage used. With repeated dosing, tipranavir plasma concentrations are lower than predicted from single dose data, presumably due to hepatic enzyme induction. Steady-state is attained in most subjects after 7 days of dosing. Tipranavir, co-administered with low dose ritonavir, exhibits linear pharmacokinetics at steady state.

Dosing with Aptivus capsules 500 mg twice daily concomitant with 200 mg ritonavir twice daily for 2 to 4 weeks and without meal restriction produced a mean tipranavir peak plasma concentration (C_{max}) of 94.8 ± 22.8 μM for female patients (n=14) and 77.6 ± 16.6 μM for male patients (n=106), occurring approximately 3 hours after administration. The mean steady-state trough concentration prior to the morning dose was 41.6 ± 24.3 μM for female patients and 35.6 ± 16.7 μM for male patients.

Tipranavir AUC over a 12 hour dosing interval averaged 851 ± 309 μM•h (CL=1.15 l/h) for female patients and 710 ± 207 μM•h (CL=1.27 l/h) for male patients. The mean half-life was 5.5 (females) or 6.0 hours (males).

Effects of food on oral absorption
Food improves the tolerability of tipranavir with ritonavir. Therefore Aptivus, co-administered with low dose ritonavir, should be given with food.

Absorption of tipranavir, co-administered with low dose ritonavir, is reduced in the presence of antacids (see section 4.5).

Distribution
Tipranavir is extensively bound to plasma proteins (>99.9%). From clinical samples of healthy volunteers and HIV-1 positive subjects who received tipranavir without ritonavir the mean fraction of tipranavir unbound in plasma was similar in both populations (healthy volunteers 0.015% ± 0.006%; HIV-positive subjects 0.019% ± 0.076%). Total plasma tipranavir concentrations for these samples ranged from 9 to 82 μM. The unbound fraction of tipranavir appeared to be independent of total concentration over this concentration range.

No studies have been conducted to determine the distribution of tipranavir into human cerebrospinal fluid or semen.

Biotransformation
In vitro metabolism studies with human liver microsomes indicated that CYP3A4 is the predominant CYP isoform involved in tipranavir metabolism.

The oral clearance of tipranavir decreased after the addition of ritonavir which may represent diminished first-pass clearance of the substance at the gastrointestinal tract as well as the liver.

The metabolism of tipranavir in the presence of low dose ritonavir is minimal. In a ^{14}C-tipranavir human study (500 mg ^{14}C-tipranavir with 200 mg ritonavir, twice daily), unchanged tipranavir was predominant and accounted for 98.4% or greater of the total plasma radioactivity circulating at 3, 8, or 12 hours after dosing. Only a few metabolites were found in plasma, and all were at trace levels (0.2% or less of the plasma radioactivity). In faeces, unchanged tipranavir represented the majority of faecal radioactivity (79.9% of faecal radioactivity). The most abundant faecal metabolite, at 4.9% of faecal radioactivity (3.2% of dose), was a hydroxyl metabolite of tipranavir. In urine, unchanged tipranavir was found in trace amounts (0.5% of urine radioactivity). The most abundant urinary metabolite, at 11.0% of urine radioactivity (0.5% of dose) was a glucuronide conjugate of tipranavir.

Elimination
Administration of ^{14}C-tipranavir to subjects (n = 8) that received 500 mg tipranavir with 200 mg ritonavir; twice daily dosed to steady-state demonstrated that most radioactivity (median 82.3%) was excreted in faeces, while only a median of 4.4% of the radioactive dose administered was recovered in urine. In addition, most radioactivity (56%) was excreted between 24 and 96 hours after dosing. The effective mean elimination half-life of tipranavir with ritonavir in healthy volunteers (n = 67) and HIV-infected adult patients (n = 120) was approximately 4.8 and 6.0 hours, respectively, at steady state following a dose of 500 mg/200 mg twice daily with a light meal.

Special populations
Although data available at this stage are currently limited to allow a definitive analysis, they suggest that the pharmacokinetic profile is unchanged in older people and comparable between races. By contrast, evaluation of the steady-state plasma tipranavir trough concentrations at 10-14 h after dosing from the RESIST-1 and RESIST-2 studies demonstrate that females generally had higher tipranavir concentrations than males. After four weeks of Aptivus 500 mg with 200 mg ritonavir (twice daily) the median plasma trough concentration of tipranavir was 43.9 μM for females and 31.1 μM for males. This difference in concentrations does not warrant a dose adjustment.

Renal impairment
Tipranavir pharmacokinetics have not been studied in patients with renal impairment. However, since the renal clearance of tipranavir is negligible, a decrease in total body clearance is not expected in patients with renal impairment.

Hepatic impairment
In a study comparing 9 patients with mild (Child-Pugh A) hepatic impairment to 9 controls, the single and multiple dose exposure of tipranavir and ritonavir were increased in patients with hepatic impairment but still within the range observed in clinical studies. No dosing adjustment is required in patients with mild hepatic impairment but patients should be closely monitored (see sections 4.2 and 4.4).

The influence of moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment on the multiple dose pharmacokinetics of either tipranavir or ritonavir has so far not been investigated. tipranavir is contraindicated in moderate or severe hepatic impairment (see sections 4.2 and 4.3).

Paediatric population
The oral solution has been shown to have greater bioavailability than the soft capsule formulation.

5.3 Preclinical safety data

Animal toxicology studies have been conducted with tipranavir alone, in mice, rats and dogs, and co-administered with ritonavir (3.75:1 w/w ratio) in rats and dogs. Studies with co-administration of tipranavir and ritonavir did not reveal any additional toxicological effects when compared to those seen in the tipranavir single agent toxicological studies.

The predominant effects of repeated administration of tipranavir across all species toxicologically tested were on the gastrointestinal tract (emesis, soft stool, diarrhoea) and the liver (hypertrophy). The effects were reversible with termination of treatment. Additional changes included bleeding in rats at high doses (rodents specific). Bleeding observed in rats was associated with prolonged prothrombin time (PT), activated partial thromboplastin time (APTT) and a decrease in some vitamin K dependent factors. The co-administration of tipranavir with vitamin E in the form of TPGS (d-alphatocopherol polyethylene glycol 1000 succinate) from 2,322 IU/m² upwards in rats resulted in a significant increase in effects on coagulation parameters, bleeding events and death. In preclinical studies of tipranavir in dogs, an effect on coagulation parameters was not seen. Co-administration of tipranavir and vitamin E has not been studied in dogs.

The majority of the effects in repeat-dose toxicity studies appeared at systemic exposure levels which are equivalent to or even below the human exposure levels at the recommended clinical dose.

In *in vitro* studies, tipranavir was found to inhibit platelet aggregation when using human platelets (see section 4.4) and thromboxane A2 binding in an in vitro cell model at levels consistent with exposure observed in patients receiving Aptivus with ritonavir. The clinical implications of these findings are not known.

In a study conducted in rats with tipranavir at systemic exposure levels (AUC) equivalent to human exposure at the recommended clinical dose, no adverse effects on mating or fertility were observed. At maternal doses producing systemic exposure levels similar to or below those at the recommended clinical dose, tipranavir did not produce teratogenic effects. At tipranavir exposures in rats at 0.8-fold human exposure at the clinical dose, foetal toxicity (decreased sternebrae ossification and body weights) was observed. In pre- and post-natal development studies with tipranavir in rats, growth inhibition of pups was observed at maternally toxic doses approximating 0.8-fold human exposure.

Carcinogenicity studies of tipranavir in mice and rats revealed tumourigenic potential specific for these species, which are regarded as of no clinical relevance. Tipranavir showed no evidence of genetic toxicity in a battery of *in vitro* and *in vivo* tests.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Macrogolglycerol ricinoleate
Ethanol
Mono/diglycerides of caprylic/capric acid
Propylene glycol
Purified water
Trometamol
Propyl gallate

Capsule shell
Gelatin
Red iron oxide (E172)
Propylene glycol
Purified water
'Sorbitol special-glycerin blend' (d-sorbitol, 1,4 sorbitan, mannitol and glycerin)
Titanium dioxide (E171)

Black printing ink
Propylene glycol
Black iron oxide (E172)
Polyvinyl acetate phthalate
Macrogol
Ammonium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

In use storage: 60 days (below 25°C), after first opening of the bottle. It is advisable that the patient writes the date of opening the bottle on the label and/or carton.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with two-piece child-resistant closure (outer and inner shell polypropylene, with a pulpboard/aluminium liner). Each bottle contains 120 soft capsules.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/315/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 October 2005
Date of latest renewal: 05 October 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Aptivus 100 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral solution contains 100 mg tipranavir.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

Clear yellow viscous liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aptivus, co-administered with low dose ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infection in highly pre-treated children from 2 to 12 years of age with virus resistant to multiple protease inhibitors. Aptivus should only be used as part of an active combination antiretroviral regimen in patients with no other therapeutic options (see sections 4.4 and 5.1).

In deciding to initiate treatment with Aptivus, co-administered with low dose ritonavir, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of Aptivus. Initiation of treatment should take into account the combinations of mutations which may negatively impact the virological response to Aptivus, co-administered with low dose ritonavir (see section 5.1).

4.2 Posology and method of administration

Aptivus must always be given with low dose ritonavir as a pharmacokinetic enhancer, and in combination with other antiretroviral medicinal products. The Summary of Product Characteristics of ritonavir must therefore be consulted prior to initiation of therapy with Aptivus (especially as regards the contraindications, warnings and undesirable effects sections).

Aptivus should be prescribed by physicians who are experienced in the treatment of HIV-1 infection.

Aptivus with ritonavir should not be used in treatment-naïve patients.

Posology
The recommended dose for children (age 2 to 12 years) is 375 mg/m^2 Aptivus co-administered with 150 mg/m^2 ritonavir, twice daily. The paediatric dose should not exceed the 500 mg/200 mg dose.

Aptivus/ritonavir dose (375 mg/m^2 Aptivus + 150 mg/m^2 ritonavir)				
BSA Range (m^2)	**Dose Aptivus (mg)**	**Volume Aptivus (ml)**	**Dose ritonavir (mg)**	**Volume ritonavir (ml)**
0.37 – 0.42	140	1.4	56	0.7
0.43 – 0.47	160	1.6	63	0.8

0.48 – 0.52	180	1.8	71	0.9
0.53 – 0.58	200	2	79	1
0.59 – 0.63	220	2.2	87	1.1
0.64 – 0.68	240	2.4	95	1.2
0.69 - 0.74	260	2.6	103	1.3
0.75 – 0.79	280	2.8	111	1.4
0.80 – 0.84	300	3	119	1.5
0.85 – 0.90	320	3.2	127	1.6
0.91 – 0.95	340	3.4	135	1.7
0.96 – 1.00	360	3.6	143	1.8
1.01 - 1.06	380	3.8	151	1.9
1.07 – 1.11	400	4	159	2
1.12 – 1.16	420	4.2	167	2.1
1.17 – 1.22	440	4.4	174	2.2
1.23 – 1.27	460	4.6	182	2.3
1.28 – 1.32	480	4.8	190	2.4
> 1.33	500	5	200	2.5

Doses of ritonavir lower than 150 mg/m^2 twice daily, should not be used as they might alter the efficacy profile of the combination.

Aptivus is available as soft capsules for adults and adolescents from 12 years of age (please refer to the respective SmPC for further details). Patients treated with Aptivus and reaching the age of 12 years should be switched to the capsule formulation (see sections 4.4 and 5.1).

Missed dose
Patients should be advised of the need to take Aptivus and ritonavir every day as prescribed. If a dose is missed by more than 5 hours, the patient should be instructed to wait and then to take the next dose of tipranavir and ritonavir at the regularly scheduled time. If a dose is missed by less than 5 hours, the patient should be instructed to take the missed dose immediately, and then to take the next dose of tipranavir and ritonavir at the regularly scheduled time.

Liver impairment
Tipranavir is metabolised by the hepatic system. Liver impairment could therefore result in an increase of tipranavir exposure and a worsening of its safety profile. Therefore, Aptivus should be used with caution, and with increased monitoring frequency, in patients with mild hepatic impairment (Child-Pugh Class A). Aptivus is contraindicated in patients with moderate or severe (Child-Pugh Class B or C) hepatic impairment (see sections 4.3, 4.4 and 5.2).

Renal impairment
No dosage adjustment is required in patients with renal impairment (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of Aptivus in children under 2 years of age has not been established. No data are available.

Method of administration
Oral use.
Aptivus oral solution co-administered with low dose oral solution ritonavir should be taken with food (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients with moderate or severe (Child-Pugh B or C) hepatic impairment.

Combination of rifampicin with Aptivus with concomitant low dose ritonavir is contraindicated (see section 4.5).

Herbal preparations containing St John's wort (*Hypericum perforatum*) due to the risk of decreased plasma concentrations and reduced clinical effects of tipranavir (see section 4.5).

Co-administration of Aptivus with low dose ritonavir, with active substances that are highly dependent on CYP3A for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These active substances include antiarrhythmics (such as amiodarone, bepridil, quinidine), antihistamines (such as astemizole, terfenadine), ergot derivatives (such as dihydroergotamine, ergonovine, ergotamine, methylergonovine), gastrointestinal motility agents (such as cisapride), antipsychotics (such as pimozide, sertindole, quetiapine), sedatives/hypnotics (such as orally administered midazolam and triazolam) and HMG-CoA reductase inhibitors (such as simvastatin and lovastatin) (see section 4.5). Also the use of the alpha-1 adrenoceptor antagonist alfuzosin, and sildenafil when used for the treatment of pulmonary arterial hypertension. In addition, co-administration of Aptivus with low dose ritonavir, and medicinal products that are highly dependent on CYP2D6 for clearance, such as the antiarrhythmics flecainide, propafenone and metoprolol given in heart failure (see section 4.5).

Co-administration of colchicine with Aptivus/ritonavir in patients with renal or hepatic impairment (see section 4.5).

4.4 Special warnings and precautions for use

Aptivus must be administered with low dose ritonavir to ensure its therapeutic effect (see section 4.2). Failure to correctly co-administer tipranavir with ritonavir will result in reduced plasma levels of tipranavir that may be insufficient to achieve the desired antiviral effect. Patients should be instructed accordingly.

Aptivus is not a cure for HIV-1 infection or AIDS. Patients receiving Aptivus or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV-1 infection.

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Switching from Aptivus capsules to the oral solution
Aptivus capsules are not interchangeable with the oral solution. Compared to the capsules, tipranavir exposure is higher when administering the same dose as oral solution. Also, the composition of the oral solution is different from that of the capsules, with the high vitamin E content being especially noteworthy. Both of these factors may contribute to an increased risk of adverse reactions (type, frequency and/or severity). Therefore patients should not be switched from Aptivus capsules to Aptivus oral solution (see sections 5.1 and 5.2).

Switching from Aptivus oral solution to the capsules
Aptivus oral solution is not interchangeable with the capsules. Compared to the oral solution, tipranavir exposure is lower when administering the same dose as capsules. However, children previously treated with Aptivus oral solution and becoming 12 years of age should be switched to capsules, particularly because of the more favourable safety profile of the capsules. It has to be noted that the switch from the oral solution to the capsule formulation of Aptivus could be associated with decreased exposure. Therefore, it is recommended that patients switching from Aptivus oral solution to capsules at the age of 12 years are closely monitored for the virologic response of their antiretroviral regimen (see sections 5.1 and 5.2).

Liver disease
Aptivus is contraindicated in patients with moderate or severe (Child-Pugh Class B or C) hepatic insufficiency. Limited data are currently available for the use of Aptivus, co-administered with low dose ritonavir, in patients co-infected with hepatitis B or C. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reaction. Aptivus should be used in this patient population only if the potential benefit outweighs the potential risk, and with increased clinical and laboratory monitoring. In the 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 mild hepatic impairment (Child-Pugh Class A) should be closely monitored.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination therapy and should be monitored according to standard practice. Aptivus with ritonavir should be discontinued once signs of worsening liver function occur in patients with pre-existing liver disease.

Aptivus co-administered with low dose ritonavir, has been associated with reports of clinical hepatitis and hepatic decompensation, including some fatalities. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medicinal products. Caution should be exercised when administering Aptivus to patients with liver enzyme abnormalities or with a history of hepatitis. Increased ALAT/ASAT monitoring should be considered in these patients.

Aptivus therapy should not be initiated in patients with pre-treatment ASAT or ALAT greater than 5 times the Upper Limit Normal (ULN) until baseline ASAT/ALAT is stabilised at less than 5X ULN, unless the potential benefit justifies the potential risk.

Aptivus therapy should be discontinued in patients experiencing ASAT or ALAT elevations greater than 10X ULN, or developing signs or symptoms of clinical hepatitis during therapy. If another cause is identified (e.g. acute hepatitis A, B or C virus, gallbladder disease, other medicinal products), then rechallenge with Aptivus may be considered when ASAT/ALAT have returned to the patient's baseline levels.

Liver monitoring
Monitoring of hepatic tests should be done prior to initiation of therapy, after two, four and then every four weeks until 24 weeks, and then every eight to twelve weeks thereafter. Increased monitoring (i.e. prior to initiation of therapy, every two weeks during the first three months of treatment, then monthly until 48 weeks, and then every eight to twelve weeks thereafter) is warranted when Aptivus and low dose ritonavir are administered to patients with elevated ASAT and ALAT levels, mild hepatic impairment, chronic hepatitis B or C, or other underlying liver disease.

Treatment-naïve patients
In a study performed in antiretroviral naïve adult patients, tipranavir 500 mg with ritonavir 200 mg twice daily, as compared to lopinavir/ritonavir, was associated with an excess in the occurrence of significant (grade 3 and 4) transaminase elevations without any advantage in terms of efficacy (trend towards a lower efficacy). The study was prematurely stopped after 60 weeks.
Therefore, tipranavir with ritonavir should not be used in treatment-naïve patients.

Renal impairment
Since the renal clearance of tipranavir is negligible, increased plasma concentrations are not expected in patients with renal impairment.

Haemophilia
There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthrosis in patients with haemophilia type A and B treated with protease inhibitors. In some patients additional Factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal

relationship has been evoked, although the mechanism of action had not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Bleeding
RESIST participants receiving Aptivus with ritonavir tended to have an increased risk of bleeding; at 24 weeks the relative risk was 1.98 (95% CI=1.03, 3.80). At 48-weeks the relative risk decreased to 1.27 (95% CI=0.76, 2.12). There was no pattern for the bleeding events and no difference between treatment groups in coagulation parameters. The significance of this finding is being further monitored.

Fatal and non-fatal intracranial haemorrhages (ICH) have been reported in patients receiving Aptivus, many of whom had other medical conditions or were receiving concomitant medicinal products that may have caused or contributed to these events. However, in some cases the role of Aptivus cannot be excluded. No pattern of abnormal haematological or coagulation parameters has been observed in patients in general, or preceding the development of ICH. Therefore, routine measurement of coagulation parameters is not currently indicated in the management of patients on Aptivus.

An increased risk of ICH has previously been observed in patients with advanced HIV disease/AIDS such as those treated in the Aptivus clinical trials.

In *in vitro* experiments, tipranavir was observed to inhibit human platelet aggregation at levels consistent with exposures observed in patients receiving Aptivus with ritonavir.

In rats, co-administration with vitamin E increased the bleeding effects of tipranavir (see section 5.3).

Aptivus, co-administered with low dose ritonavir, should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other medical conditions, or who are receiving medicinal products known to increase the risk of bleeding such as antiplatelet agents and anticoagulants or who are taking supplemental vitamin E. Patients taking Aptivus oral solution should be advised not to take any supplemental vitamin E.

Diabetes mellitus/hyperglycaemia
New onset of diabetes mellitus, hyperglycaemia or exacerbations of existing diabetes mellitus has been reported in patients receiving antiretroviral therapy, including protease inhibitors. In some of these the hyperglycaemia was severe and in some cases also associated with ketoacidosis. Many of the patients had confounding medical conditions, some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycaemia.

Lipid elevations
Treatment with Aptivus co-administered with low dose ritonavir and other antiretroviral agents has resulted in increased plasma total triglycerides and cholesterol. Triglyceride and cholesterol testing should be performed prior to initiating tipranavir therapy and during therapy. Treatment-related lipid elevations should be managed as clinically appropriate.

Fat redistribution
Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV infected patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors, and lipoatrophy and nucleoside reverse transcriptase inhibitors, has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with factors related to the active substance such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

Immune reactivation syndrome
In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and pneumocystis pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. In addition, reactivation of herpes simplex and herpes zoster has been observed in clinical studies with Aptivus, co-administered with low dose ritonavir.

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Rash
Mild to moderate rashes including urticarial rash, maculopapular rash, and photosensitivity have been reported in subjects receiving Aptivus, co-administered with low dose ritonavir. At 48-weeks in Phase III trials, rash of various types was observed in 15.5% males and 20.5% females receiving Aptivus co-administered with low dose ritonavir. Additionally, in one interaction trial, in healthy female volunteers administered a single dose of ethinyl oestradiol followed by Aptivus co-administered with low dose ritonavir, 33% of subjects developed a rash. Rash accompanied by joint pain or stiffness, throat tightness, or generalized pruritus has been reported in both men and women receiving Aptivus co-administered with low dose ritonavir. In the paediatric clinical trial, the frequency of rash (all grades, all causality) through 48 weeks of treatment was higher than in adult patients.

Osteonecrosis
Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Interactions
The interaction profile of tipranavir, co-administered with low dose ritonavir, is complex. The mechanisms and potential mechanisms contributing to the interaction profile of tipranavir are described (see section 4.5).

Abacavir and zidovudine
The concomitant use of Aptivus, co-administered with low dose ritonavir, with zidovudine or abacavir, results in a significant decrease in plasma concentration of these nucleoside reverse transcriptase inhibitors (NRTIs). Therefore, the concomitant use of zidovudine or abacavir with Aptivus, co-administered with low dose ritonavir, is not-recommended unless there are no other available NRTIs suitable for patient management (see section 4.5).

Protease inhibitors
Concomitant use of Aptivus, co-administered with low dose ritonavir, with the protease inhibitors amprenavir, lopinavir or saquinavir (each co-administered with low dose ritonavir) in a dual-boosted regimen, results in significant decreases in plasma concentrations of these protease inhibitors. A significant decrease in plasma concentrations of atazanavir and a marked increase of tipranavir and ritonavir concentrations was observed when Aptivus, associated with low dose ritonavir, was co-administered with atazanavir (see section 4.5). No data are currently available on interactions of tipranavir, co-administered with low dose ritonavir, with protease inhibitors other than those listed above. Therefore, the co-administration of tipranavir, co-administered with low dose ritonavir, with protease inhibitors is not recommended.

Oral contraceptives and oestrogens
Since levels of ethinyl oestradiol are decreased, the co-administration of Aptivus co-administered with low dose ritonavir is not recommended. Alternative or additional contraceptive measures are to be used when oestrogen based oral contraceptives are co-administered with Aptivus co-administered with low dose ritonavir (see section 4.5). Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency. Women using oestrogens may have an increased risk of non serious rash.

Anticonvulsants
Caution should be used when prescribing carbamazepine, phenobarbital, and phenytoin. Aptivus may be less effective due to decreased tipranavir plasma concentrations in patients taking these agents concomitantly.

Halofantrine, lumefantrine
Due to their metabolic profile and inherent risk of inducing torsades de pointes, administration of halofantrine and lumefantrine with Aptivus co-administered with low dose ritonavir, is not recommended.

Fluticasone
Concomitant use of tipranavir, co-administered with low dose ritonavir, and fluticasone or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see section 4.5).

Atorvastatin
Tipranavir, co-administered with low dose ritonavir, increases the plasma concentrations of atorvastatin (see section 4.5). The combination is not recommended. Other HMG-CoA reductase inhibitors should be considered such as pravastatin, fluvastatin or rosuvastatin (see section 4.5). However, if atorvastatin is specifically required for patient management, it should be started with the lowest dose and careful monitoring is necessary.

Omeprazole and other proton pump inhibitors
The combined use of Aptivus with ritonavir with either omeprazole, esomeprazole or with other proton pump inhibitors is not recommended (see section 4.5).

Colchicine
In patients with normal renal and hepatic function, a reduction in colchicine dosage or an interruption of colchicine treatment is recommended in co-administration (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.

4.5 Interaction with other medicinal products and other forms of interaction

The interaction profile of Aptivus, co-administered with low dose ritonavir, is complex and requires special attention in particular in combination with other antiretroviral agents.

Interaction studies have only been performed in adults.

Metabolic profile of tipranavir

Tipranavir is a substrate, an inducer and an inhibitor of cytochrome P450 CYP3A. When co-administered with ritonavir at the recommended dosage (see section 4.2) there is a net inhibition of P450 CYP3A. Co-administration of Aptivus and low dose ritonavir with agents primarily metabolised by CYP3A may result in changed plasma concentrations of tipranavir or the other agents, which could alter their therapeutic and undesirable effects (see list and details of considered agents, below). Agents that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse reactions are detailed in this section, and listed in section 4.3.

A cocktail study was conducted in 16 healthy volunteers with twice-daily tipranavir 500 mg with ritonavir 200 mg capsule administration for 10 days to assess the net effect on the activity of hepatic CYP 1A2 (caffeine), 2C9 (warfarin), 2D6 (dextromethorphan), both intestinal/hepatic CYP 3A4 (midazolam) and P-glycoprotein (P-gp) (digoxin). At steady state, there was a significant induction of CYP 1A2 and a slight induction on CYP 2C9. Potent inhibition of CYP 2D6 and both hepatic and intestinal CYP 3A4 activities were observed. P-gp activity is significantly inhibited after the first dose, but there was a slight induction at steady state. Practical recommendations deriving from this study are displayed below. This study was also conducted with Aptivus oral solution 500 mg with ritonavir 200 mg and showed the same CYP P450 and P-gp interactions as the Aptivus capsule 500 mg with ritonavir 200 mg. Based on the results from this study, Aptivus oral solution might be expected to have a similar interaction profile as the capsules.

Studies in human liver microsomes indicated tipranavir is an inhibitor of CYP 1A2, CYP 2C9, CYP 2C19 and CYP 2D6. The potential net effect of tipranavir with ritonavir on CYP 2D6 is inhibition, because ritonavir is also a CYP 2D6 inhibitor. The *in vivo* net effect of tipranavir with ritonavir on CYP 1A2, CYP 2C9 and CYP 2C19, indicates, through a preliminary study, an inducing potential of tipranavir with ritonavir on CYP1A2 and, to a lesser extent, on CYP2C9 and P-gp after several days of treatment. Data are not available to indicate whether tipranavir inhibits or induces glucuronosyl transferases.

In vitro studies show that tipranavir is a substrate and also an inhibitor of P-gp.

It is difficult to predict the net effect of Aptivus co-administered with low dose ritonavir on oral bioavailability and plasma concentrations of agents that are dual substrates of CYP3A and P-gp. The net effect will vary depending on the relative affinity of the co-administered substance for CYP3A and P-gp, and the extent of intestinal first-pass metabolism/efflux.

Co-administration of Aptivus and agents that induce CYP3A and/or P-gp may decrease tipranavir concentrations and reduce its therapeutic effect (see list and details of considered agents, below). Co-administration of Aptivus and medicinal products that inhibit P-gp may increase tipranavir plasma concentrations.

Known and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in the table below.

Interaction table

Interactions between Aptivus and co-administered medicinal products are listed in the table below (increase is indicated as "↑", decrease as "↓", no change as "↔",once daily as "QD", twice daily as "BID").

Unless otherwise stated, studies detailed below have been performed with the recommended dosage of Aptivus/r (i.e. 500/200 mg BID). However, some PK interaction studies were not performed with this recommended dosage. Nevertheless, the results of many of these interaction studies can be extrapolated to the recommended dosage since the doses used (eg. TPV/r 500/100 mg, TPV/r 750/200 mg) represented extremes of hepatic enzyme induction and inhibition and bracketed the recommended dosage of Aptivus/r.

Drugs by Therapeutic Area	Interaction Geometric mean change (%)	Recommendations concerning co-administration
Anti-infectives		
Antiretrovirals		
Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)		
Since there is no significant impact of nucleoside and nucleotide analogues on the P450 enzyme system no dosage adjustment of Aptivus is required when co-administered with these agents.		
Abacavir 300 mg BID (TPV/r 750/100 mg BID)	Abacavir C_{max} ↓ 46% Abacavir AUC ↓ 36% The clinical relevance of this reduction has not been established, but may decrease the efficacy of abacavir. Mechanism unknown.	The concomitant use of Aptivus, co-administered with low dose ritonavir, with abacavir is not recommended unless there are no other available NRTIs suitable for patient management. In such cases no dosage adjustment of abacavir can be recommended (see section 4.4).
Didanosine 200 mg BID, ≥ 60 kg - 125 mg BID, < 60 kg (TPV/r 250/200 mg BID) (TPV/r 750/100 mg BID)	Didanosine C_{max} ↓ 43% Didanosine AUC ↓ 33% Didanosine C_{max} ↓ 24% Didanosine AUC ↔ The clinical relevance of this reduction in didanosine concentrations has not been established. Mechanism unknown.	Dosing of enteric-coated didanosine and Aptivus soft capsules, co-administered with low dose ritonavir, should be separated by at least 2 hours to avoid formulation incompatibility.
Emtricitabine No interaction study performed	Potential interactions with renal transporters cannot be fully excluded.	No dosage adjustment necessary in patients with normal renal function. In case of concomitant administration of emtricitabine and Aptivus/ritonavir, renal function should be evaluated before initiating the co-administration.
Lamivudine 150 mg BID (TPV/r 750/100 mg BID)	No clinically significant interaction is observed.	No dosage adjustment necessary.
Stavudine 40 mg BID ≥ 60 kg 30 mg BID < 60 kg (TPV/r 750/100 mg BID)	No clinically significant interaction is observed.	No dosage adjustment necessary.
Zidovudine 300 mg BID (TPV/r 750/100 mg BID)	Zidovudine C_{max} ↓ 49% Zidovudine AUC ↓ 36% The clinical relevance of this reduction has not been established, but may decrease the efficacy of zidovudine. Mechanism unknown.	The concomitant use of Aptivus, co-administered with low dose ritonavir with zidovudine is not recommended unless there are no other available NRTIs suitable for patient management. In such cases no dosage adjustment of zidovudine can be recommended (see section 4.4).
Tenofovir 300 mg QD (TPV/r 750/200 mg BID)	No clinically significant interaction is observed.	No dosage adjustment necessary.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz 600 mg QD	No clinically significant interaction is observed.	No dosage adjustment necessary.
Etravirine	Etravirine C_{max} ↓ 71% Etravirine AUC ↓ 76% Etravirine C_{min} ↓ 82% Concomitant use of Aptivus/ritonavir caused a decrease of etravirine exposure that could significantly impair the virologic response to etravirine.	Co-administration of etravirine and Aptivus/ritonavir is not recommended.
Nevirapine No interaction study performed	The limited data available from a phase IIa study in HIV-infected patients suggest that no significant interaction is expected between nevirapine and TPV/r. Moreover a study with TPV/r and another NNRTI (efavirenz) did not show any clinically relevant interaction (see above).	No dosage adjustment necessary.
Rilpivirine No interaction study performed	Concomitant use of rilpivirine with some ritonavir-boosted protease inhibitors has demonstrated an increase in the plasma concentrations of rilpivirine.	Close monitoring for signs of rilpivirine toxicity and possibly also dose adjustment of rilpivirine is recommended when co-administered with Aptivus/ritonavir.
Protease inhibitors (PIs)		
<u>According to current treatment guidelines, dual therapy with protease inhibitors is generally not recommended</u>		
Amprenavir/ritonavir 600/100 mg BID	Amprenavir C_{max} ↓ 39% Amprenavir AUC ↓ 44% Amprenavir C_{min} ↓ 55% The clinical relevance of this reduction in amprenavir concentrations has not been established. Mechanism unknown.	The concomitant use of Aptivus, co-administered with low dose ritonavir, with amprenavir/ritonavir is not recommended. If the combination is nevertheless considered necessary, a monitoring of the plasma levels of amprenavir is strongly encouraged (see section 4.4).
Atazanavir/ritonavir 300/100 mg QD (TPV/r 500/100 mg BID)	Atazanavir C_{max} ↓ 57% Atazanavir AUC ↓ 68% Atazanavir C_{min} ↓ 81% Mechanism unknown. Tipranavir C_{max} ↑ 8% Tipranavir AUC ↑ 20% Tipranavir C_{min} ↑ 75% Inhibition of CYP 3A4 by atazanavir/ritonavir and induction by tipranavir/r.	The concomitant use of Aptivus, co-administered with low dose ritonavir, with atazanavir/ritonavir is not recommended. If the co-administration is nevertheless considered necessary, a close monitoring of the safety of tipranavir and a monitoring of plasma concentrations of atazanavir are strongly encouraged (see section 4.4).
Lopinavir/ritonavir 400/100 mg BID	Lopinavir C_{max} ↓ 47% Lopinavir AUC ↓ 55% Lopinavir C_{min} ↓ 70%	The concomitant use of Aptivus, co-administered with low dose ritonavir, with lopinavir/ritonavir is not recommended.

	The clinical relevance of this reduction in lopinavir concentrations has not been established. Mechanism unknown.	If the combination is nevertheless considered necessary, a monitoring of the plasma levels of lopinavir is strongly encouraged (see section 4.4).
Saquinavir/ritonavir 600/100 mg QD	Saquinavir C_{max} ↓ 70% Saquinavir AUC ↓ 76% Saquinavir C_{min} ↓ 82% The clinical relevance of this reduction in saquinavir concentrations has not been established. Mechanism unknown.	The concomitant use of Aptivus, co-administered with low dose ritonavir, with saquinavir/ritonavir is not recommended. If the combination is nevertheless considered necessary, a monitoring of the plasma levels of saquinavir is strongly encouraged (see section 4.4).
Protease inhibitors other than those listed above	No data are currently available on interactions of tipranavir, co-administered with low dose ritonavir, with protease inhibitors other than those listed above.	Combination with Aptivus, co-administered with low dose ritonavir, is not recommended (see section 4.4)
Fusion inhibitors		
Enfuvirtide No interaction study performed	In studies where tipranavir co-administered with low-dose ritonavir was used with or without enfuvirtide, it has been observed that the steady-state plasma tipranavir trough concentration of patients receiving enfuvirtide were 45% higher as compared to patients not receiving enfuvirtide. No information is available for the parameters AUC and C_{max}. A pharmacokinetic interaction is mechanistically unexpected and the interaction has not been confirmed in a controlled interaction study.	The clinical impact of the observed data, especially regarding the tipranavir with ritonavir safety profile, remains unknown. Nevertheless, the clinical data available from the RESIST trials did not suggest any significant alteration of the tipranavir with ritonavir safety profile when combined with enfuvirtide as compared to patients treated with tipranavir with ritonavir without enfuvirtide.
Integrase strand transfer inhibitors		
Raltegravir 400 mg BID	Raltegravir C_{max} ↔ 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.
Pharmacokinetic enhancer		
Cobicistat and cobicistat-containing products	When co-administered, tipranavir and cobicistat exposures are markedly lower compared to that of tipranavir when boosted with low dose ritonavir.	Aptivus/ritonavir should not be administered concomitantly with cobicistat or cobicistat-containing products.

Anti-HCV agents		
Boceprevir No interaction study performed	In a pharmacokinetic study of healthy volunteers, boceprevir decreased the exposure of ritonavir, and some ritonavir-boosted protease inhibitors. Boceprevir exposure was reduced when co-administered with ritonavir-boosted lopinavir or ritonavir-boosted darunavir. These drug-drug interactions may reduce the effectiveness of HIV protease inhibitors and/or boceprevir when co-administered.	Co-administration of boceprevir with Aptivus/ritonavir is not recommended.
Telaprevir No interaction study performed	Telaprevir is metabolized in the liver by CYP3A and is a P-glycoprotein (P-gp) substrate, but other enzymes may be involved in the metabolism. When Aptivus/ritonavir is co-administered with telaprevir, a decrease or an increase of telaprevir exposure could be expected. There is a heterogeneous effect of telaprevir on ritonavir-boosted protease inhibitor drug plasma levels, depending on the protease inhibitors. Therefore, a modification of Aptivus exposure cannot be ruled out.	Co-administration of telaprevir with Aptivus/ritonavir is not recommended.
Antifungals		
Fluconazole 200 mg QD (Day 1) then 100 mg QD	Fluconazole ↔ Tipranavir C_{max} ↑ 32% Tipranavir AUC ↑ 50% Tipranavir C_{min} ↑ 69% Mechanism unknown	No dosage adjustments are recommended. Fluconazole doses >200 mg/day are not recommended.
Itraconazole **Ketoconazole** No interaction study performed	Based on theoretical considerations tipranavir, co-administered with low dose ritonavir, is expected to increase itraconazole or ketoconazole concentrations. Based on theoretical considerations, tipranavir or ritonavir concentrations might increase upon co-administration with itraconazole or ketoconazole.	Itraconazole or ketoconazole should be used with caution (doses >200 mg/day are not recommended).
Voriconazole No interaction study performed	Due to multiple CYP isoenzyme systems involved in voriconazole metabolism, it is difficult to predict the interaction with tipranavir, co-administered with low-dose ritonavir.	Based on the known interaction of voriconazole with low dose ritonavir (see voriconazole SmPC) the co-administration of tipranavir/r and voriconazole should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.

Anti-gouts		
Colchicine No interaction study performed	Based on theoretical considerations, colchicine concentrations may increase upon co-administration with tipranavir and low dose ritonavir, due to tipranavir/ritonavir CYP3A and P-gp inhibition. However a decrease of colchicine concentrations cannot be excluded since both tipranavir and ritonavir exhibit inducing potential towards CYP3A and P-gp. Colchicine is a substrate of CYP3A4 and P-gp (an intestinal efflux transporter).	A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with Aptivus/ritonavir is required (see section 4.4). In patients with renal or hepatic impairment, co-administration of colchicine in patients on Aptivus/ritonavir is contraindicated (see section 4.3).
Antibiotics		
Clarithromycin 500 mg BID	Clarithromycin C_{max} ↔ Clarithromycin AUC ↑ 19% Clarithromycin C_{min} ↑ 68% 14-OH-clarithromycin C_{max} ↓ 97% 14-OH-clarithromycin AUC ↓ 97% 14-OH-clarithromycin C_{min} ↓ 95% Tipranavir C_{max} ↑ 40% Tipranavir AUC ↑ 66% Tipranavir C_{min} ↑ 100% CYP 3A4 inhibition by tipranavir/r and P-gp (an intestinal efflux transporter) inhibition by clarithromycin.	Whilst the changes in clarithromycin parameters are not considered clinically relevant, the reduction in the 14-OH metabolite AUC should be considered for the treatment of infections caused by *Haemophilus influenzae* in which the 14-OH metabolite is most active. The increase of tipranavir C_{min} may be clinically relevant. Patients using clarithromycin at doses higher than 500 mg twice daily should be carefully monitored for signs of toxicity of clarithromycin and tipranavir. For patients with renal impairment dose reduction of clarithromycin should be considered (see clarithromycin and ritonavir product information).
Rifabutin 150 mg QD	Rifabutin C_{max} ↑ 70% Rifabutin AUC ↑ 190% Rifabutin C_{min} ↑ 114% 25-O-desacetylrifabutin C_{max} ↑ 3.2 fold 25-O-desacetylrifabutin AUC ↑ 21 fold 25-O-desacetylrifabutin C_{min} ↑ 7.8 fold Inhibition of CYP 3A4 by tipranavir/r No clinically significant change is observed in tipranavir PK parameters.	Dosage reductions of rifabutin by at least 75% of the usual 300 mg/day are recommended (ie 150 mg on alternate days, or three times per week). Patients receiving rifabutin with Aptivus, co-administered with low dose ritonavir, should be closely monitored for emergence of adverse events associated with rifabutin therapy. Further dosage reduction may be necessary.
Rifampicin	Co-administration of protease inhibitors with rifampicin substantially decreases protease inhibitor concentrations. In the case	Concomitant use of Aptivus, co-administered with low dose ritonavir, and rifampicin is contraindicated (see section 4.3).

	of tipranavir co-administered with low dose ritonavir, concomitant use with rifampicin is expected to result in sub-optimal levels of tipranavir which may lead to loss of virologic response and possible resistance to tipranavir.	Alternate antimycobacterial agents such as rifabutin should be considered.
Antimalarial		
Halofantrine **Lumefantrine** No interaction study performed	Based on theoretical considerations, tipranavir, co-administered with low dose ritonavir, is expected to increase halofantrine and lumefantrine concentrations. Inhibition of CYP 3A4 by tipranavir/r	Due to their metabolic profile and inherent risk of inducing torsades de pointes, administration of halofantrine and lumefantrine with Aptivus, co-administered with low dose ritonavir, is not recommended (see section 4.4).
Anticonvulsants		
Carbamazepine 200 mg BID	Carbamazepine total* C_{max} ↑ 13% Carbamazepine total* AUC ↑ 16% Carbamazepine total* C_{min} ↑ 23% *Carbamazepine total = total of carbamazepine and epoxy-carbamazepine (both are pharmacologically active moieties). The increase in carbamazepine total PK parameters is not expected to have clinical consequences. Tipranavir C_{min} ↓ 61% (compared to historical data) The decrease in tipranavir concentrations may result in decreased effectiveness. Carbamazepine induces CYP3A4.	Carbamazepine should be used with caution in combination with Aptivus, co-administered with low dose ritonavir. Higher doses of carbamazepine (> 200 mg) may result in even larger decreases in tipranavir plasma concentrations (see section 4.4).
Phenobarbital **Phenytoin** No interaction study performed	Phenobarbital and phenytoin induce CYP3A4.	Phenobarbital and phenytoin should be used with caution in combination with Aptivus, co-administered with low dose ritonavir (see section 4.4).
Antispasmodic		
Tolterodine No interaction study performed	Based on theoretical considerations, tipranavir, co-administered with low dose ritonavir, is expected to increase tolterodine concentrations. Inhibition of CYP 3A4 and CYP 2D6 by tipranavir/r	Co-administration is not recommended.
Endothelin receptor antagonists		
Bosentan	Based on theoretical considerations, bosentan concentrations may increase upon co-administration with tipranavir and low dose ritonavir.	Co-administration of bosentan and Aptivus with low dose ritonavir is not recommended (see section 4.4).

	Inhibition of CYP 3A4 by tipranavir/r	
HMG CoA reductase inhibitors		
Atorvastatin 10 mg QD	Atorvastatin C_{max} ↑ 8.6 fold Atorvastatin AUC ↑ 9.4 fold Atorvastatin C_{min} ↑ 5.2 fold Tipranavir ↔ Inhibition of CYP 3A4 by tipranavir/r	Co-administration of atorvastatin and Aptivus, co-administered with low dose ritonavir, is not recommended. Other HMG-CoA reductase inhibitors should be considered such as pravastatin, fluvastatin or rosuvastatin (See also section 4.4 and rosuvastatin and pravastatin recommendations). In cases where co-administration is necessary, the dose of 10 mg atorvastatin daily should not be exceeded. It is recommended to start with the lowest dose and careful clinical monitoring is necessary (see section 4.4).
Rosuvastatin 10 mg QD	Rosuvastatin C_{max} ↑ 123% Rosuvastatin AUC ↑ 37% Rosuvastatin C_{min} ↑ 6% Tipranavir ↔ Mechanism unknown.	Co-administration of Aptivus, co-administered with low dose ritonavir, and rosuvastatin should be initiated with the lowest dose (5 mg/day) of rosuvastatin, titrated to treatment response, and accompanied with careful clinical monitoring for rosuvastatin associated symptoms as described in the label of rosuvastatin.
Pravastatin No interaction study performed	Based on similarities in the elimination between pravastatin and rosuvastatin, TPV/r could increase the plasma levels of pravastatin. Mechanism unknown.	Co-administration of Aptivus, co-administered with low dose ritonavir, and pravastatin should be initiated with the lowest dose (10 mg/day) of pravastatin, titrated to treatment response, and accompanied with careful clinical monitoring for pravastatin associated symptoms as described in the label of pravastatin.
Simvastatin **Lovastatin** No interaction study performed	The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A for metabolism.	The concomitant use of Aptivus, co-administered with low dose ritonavir, with simvastatin or lovastatin are contra-indicated due to an increased risk of myopathy, including rhabdomyolysis (see section 4.3).
HERBAL PRODUCTS		
St. John's wort (*Hypericum perforatum*) No interaction study performed	Plasma concentrations of tipranavir can be reduced by concomitant use of the herbal preparation St John's wort (*Hypericum perforatum*). This is due to induction of drug metabolising enzymes by St John's wort.	Herbal preparations containing St. John's wort must not be combined with Aptivus, co-administered with low dose ritonavir. Co-administration of Aptivus with ritonavir, with St. John's wort is expected to substantially decrease tipranavir and ritonavir concentrations and may result in

		sub-optimal levels of tipranavir and lead to loss of virologic response and possible resistance to tipranavir.
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.
Oral contraceptives / Oestrogens		
Ethinyl oestradiol 0.035 mg / **Norethindrone** 1.0 mg QD (TPV/r 750/200 mg BID)	Ethinyl oestradiol C_{max} ↓ 52% Ethinyl oestradiol AUC ↓ 43% Mechanism unknown Norethindrone C_{max} ↔ Norethindrone AUC ↑ 27% Tipranavir ↔	The concomitant administration with Aptivus, co-administered with low dose ritonavir, is not recommended. Alternative or additional contraceptive measures are to be used when oestrogen based oral contraceptives are co-administered with Aptivus and low dose ritonavir. Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency (see sections 4.4 and 4.6).
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). Co-administration of Aptivus/ritonavir with sildenafil, when used to treat pulmonary arterial hypertension, is contraindicated.
Tadalafil 10 mg QD	Tadalafil first-dose C_{max} ↓ 22% Tadalafil first-dose AUC ↑ 133% CYP 3A4 inhibition and induction by tipranavir/r	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

	Tadalafil steady-state C_{max} ↓ 30% Tadalafil steady-state AUC ↔ No clinically significant change is observed in tipranavir PK parameters.	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).
Narcotic analgesics		
Methadone 5 mg QD	Methadone C_{max} ↓ 55% Methadone AUC ↓ 53% Methadone C_{min} ↓ 50% R-methadone C_{max} ↓ 46% R-methadone AUC ↓ 48% S-methadone C_{max} ↓ 62% S-methadone AUC ↓ 63% Mechanism unknown	Patients should be monitored for opiate withdrawal syndrome. Dosage of methadone may need to be increased.
Meperidine No interaction study performed	Tipranavir, co-administered with low dose ritonavir, is expected to decrease meperidine concentrations and increase normeperidine metabolite concentrations.	Dosage increase and long-term use of meperidine with Aptivus, co-administered with low dose ritonavir, are not recommended due to the increased concentrations of the metabolite normeperidine which has both analgesic activity and CNS stimulant activity (e.g. seizures).
Buprenorphine/Naloxone	Buprenorphine ↔ Norbuprenorphine AUC ↓ 79% Norbuprenorphine C_{max} ↓ 80% Norbuprenorphine C_{min} ↓ 80%	Due to reduction in the levels of the active metabolite norbuprenorphine, co-administration of Aptivus, co-administered with low dose ritonavir, and buprenorphine/naloxone may result in decreased clinical efficacy of buprenorphine. Therefore, patients should be monitored for opiate withdrawal syndrome.
Immunosupressants		
Cyclosporin **Tacrolimus** **Sirolimus** No interaction study performed	Concentrations of cyclosporin, tacrolimus, or sirolimus cannot be predicted when co-administered with tipranavir co-administered with low dose ritonavir, due to conflicting effect of tipranavir, co-administered with low dose ritonavir, on CYP 3A and P-gp.	More frequent concentration monitoring of these medicinal products is recommended until blood levels have been stabilised.
Antithrombotics		
Warfarin 10 mg QD	First-dose tipranavir /r: S-warfarin C_{max} ↔ S-warfarin AUC ↑ 18% Steady-state tipranavir/r: S-warfarin C_{max} ↓ 17% S-warfarin AUC ↓ 12% Inhibition of CYP 2C9 with first-dose tipranavir /r, then induction of	Aptivus, co-administered with low dose ritonavir, when combined with warfarin may be associated with changes in INR (International Normalised Ratio) values, and may affect anticoagulation (thrombogenic effect) or increase the risk of bleeding. Close clinical and biological (INR measurement) monitoring is recommended when

	CYP 2C9 with steady-state tipranavir/r	warfarin and tipranavir are combined.
Antacids		
aluminium- and magnesium-based antacid QD	Tipranavir C_{max} ↓ 25% Tipranavir AUC ↓ 27% Mechanism unknown	Dosing of Aptivus, co-administered with low dose ritonavir, with antacids should be separated by at least a two hours time interval.
Proton pump inhibitors (PPIs)		
Omeprazole 40 mg QD	Omeprazole C_{max} ↓ 73% Omeprazole AUC ↓ 70% Similar effects were observed for the S-enantiomer, esomeprazole. Induction of CYP 2C19 by tipranavir/r Tipranavir ↔	The combined use of Aptivus, co-administered with low dose ritonavir, with either omeprazole or esomeprazole is not recommended (see section 4.4). If unavoidable, upward dose adjustments for either omeprazole or esomeprazole may be considered based on clinical response to therapy. There are no data available indicating that omeprazole or esomeprazole dose adjustments will overcome the observed pharmacokinetic interaction. Recommendations for maximal doses of omeprazole or esomeprazole are found in the corresponding product information. No tipranavir with ritonavir dose adjustment is required.
Lansoprazole **Pantoprazole** **Rabeprazole** No interaction study performed	Based on the metabolic profiles of tipranavir/r and the proton pump inhibitors, an interaction can be expected. As a result of CYP3A4 inhibition and CYP2C19 induction by tipranavir/r, lansoprazole and pantoprazole plasma concentrations are difficult to predict. Rabeprazole plasma concentrations might decrease as a result of induction of CYP2C19 by tipranavir/r.	The combined use of Aptivus, co-administered with low dose ritonavir, with proton pump inhibitors is not recommended (see section 4.4). If the co-administration is judged unavoidable, this should be done under close clinical monitoring.
H2-receptor antagonists		
No interaction study performed	No data are available for H2-receptor antagonists in combination with tipranavir and low dose ritonavir.	An increase in gastric pH that may result from H2-receptor antagonist therapy is not expected to have an impact on tipranavir plasma concentrations.
Antiarrhythmics		
Amiodarone **Bepridil** **Quinidine** No interaction study performed	Based on theoretical considerations, tipranavir, co-administered with low dose ritonavir, is expected to increase amiodarone, bepridil and quinidine concentrations. Inhibition of CYP 3A4 by tipranavir/r	The concomitant use of Aptivus, co-administered with low dose ritonavir, with amiodarone, bepridil or quinidine is contraindicated due to potential serious and/or life threatening events (see section 4.3)

Flecainide **Propafenone** **Metoprolol** (given in heart failure) No interaction study performed	Based on theoretical considerations, tipranavir, co-administered with low dose ritonavir, is expected to increase flecainide, propafenone and metoprolol concentrations. Inhibition of CYP 2D6 by tipranavir/r	The concomitant use of Aptivus, co-administered with low dose ritonavir, with flecainide, propafenone or metoprolol is contraindicated (see section 4.3)
Antihistamines		
Astemizole **Terfenadine** No interaction study performed	Based on theoretical considerations, tipranavir, co-administered with low dose ritonavir, is expected to increase astemizole and terfenadine concentrations. Inhibition of CYP 3A4 by tipranavir/r	The concomitant use of Aptivus, co-administered with low dose ritonavir, with astemizole or terfenadine is contraindicated due to potential serious and/or life threatening events (see section 4.3)
Ergot derivatives		
Dihydroergotamine **Ergonovine** **Ergotamine** **Methylergonovine** No interaction study performed	Based on theoretical considerations, tipranavir, co-administered with low dose ritonavir, is expected to increase dihydroergotamine, ergonovine, ergotamine and methylergonovine concentrations. Inhibition of CYP 3A4 by tipranavir/r	The concomitant use of Aptivus, co-administered with low dose ritonavir, with dihydroergotamine, ergonovine, ergotamine or methylergonovine is contraindicated due to potential serious and/or life threatening events (see section 4.3)
Gastrointestinal motility agents		
Cisapride No interaction study performed	Based on theoretical considerations, tipranavir, co-administered with low dose ritonavir, is expected to increase cisapride concentrations. Inhibition of CYP 3A4 by tipranavir/r	The concomitant use of Aptivus, co-administered with low dose ritonavir, with cisapride is contraindicated due to potential serious and/or life threatening events (see section 4.3)
Antipsychotics		
Pimozide **Sertindole** **Quetiapine** No interaction study performed	Based on theoretical considerations, tipranavir, co-administered with low dose ritonavir, is expected to increase pimozide, sertindole and quetiapine concentrations. Inhibition of CYP 3A4 by tipranavir/r	The concomitant use of Aptivus, co-administered with low dose ritonavir, with pimozide, sertindole, or quetiapine is contraindicated due to potential serious and/or life threatening events, including coma (see section 4.3)
Sedatives/hypnotics		
Midazolam 2 mg QD (iv) **Midazolam** 5 mg QD (po)	First-dose tipranavir/r: Midazolam C_{max} ↔ Midazolam AUC ↑ 5.1 fold Steady-state tipranavir/r: Midazolam C_{max} ↓ 13% Midazolam AUC ↑ 181% First-dose tipranavir/r Midazolam C_{max} ↑ 5.0 fold Midazolam AUC ↑ 27 fold	Concomitant use of Aptivus, co-administered with low dose ritonavir, and oral midazolam is contra-indicated (see section 4.3). If Aptivus with ritonavir is administered with parenteral midazolam, close clinical monitoring for respiratory depression and/or prolonged sedation should be instituted and dosage adjustment should be

	Steady-state tipranavir/r Midazolam C_{max} ↑ 3.7 fold Midazolam AUC ↑ 9.8 fold Ritonavir is a potent inhibitor of CYP3A4 and therefore affect drugs metabolised by this enzyme.	considered.
Triazolam No interaction study performed	Based on theoretical considerations, tipranavir, co-administered with low dose ritonavir, is expected to increase triazolam concentrations. Inhibition of CYP 3A4 by tipranavir/r	The concomitant use of Aptivus, co-administered with low dose ritonavir, with triazolam is contraindicated due to potential serious and/or life threatening events (see section 4.3)
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 of 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.
Others		
Theophylline No interaction study performed	Based on data from the cocktail study where caffeine (CYP1A2 substrate) AUC was reduced by 43%, tipranavir with ritonavir is expected to decrease theophylline concentrations. Induction of CYP 1A2 by tipranavir/r	Theophylline plasma concentrations should be monitored during the first two weeks of co-administration with Aptivus, co-administered with low dose ritonavir, and the theophylline dose should be increased as needed.
Desipramine No interaction study performed	Tipranavir, co-administered with low dose ritonavir, is expected to increase desipramine concentrations Inhibition of CYP 2D6 by tipranavir/r	Dosage reduction and concentration monitoring of desipramine is recommended.
Digoxin 0.25 mg QD iv **Digoxin** 0.25 mg QD po	First-dose tipranavir/r Digoxin C_{max} ↔ Digoxin AUC ↔ Steady-state tipranavir/r Digoxin C_{max} ↓ 20% Digoxin AUC ↔ First-dose tipranavir/r	Monitoring of digoxin serum concentrations is recommended until steady state has been obtained.

	Digoxin C_{max} ↑ 93% Digoxin AUC ↑ 91% Transient inhibition of P-gp by tipranavir/r, followed by induction of P-gp by tipranavir/r at steady-state Steady-state tipranavir/r Digoxin C_{max} ↓ 38% Digoxin AUC ↔	
Trazodone Interaction study performed only with ritonavir	In a pharmacokinetic study performed in healthy volunteers, concomitant use of low dose ritonavir (200 mg twice daily) with a single dose of trazodone led to an increased plasma concentration of trazodone (AUC increased by 2.4 fold). Adverse events of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir in this study. However, it is unknown whether the combination of tipranavir with ritonavir might cause a larger increase in trazodone exposure.	The combination should be used with caution and a lower dose of trazodone should be considered.
Bupropion 150 mg BID	Bupropion C_{max} ↓ 51% Bupropion AUC ↓ 56% Tipranavir ↔ The reduction of bupropion plasma levels is likely due to induction of CYP2B6 and UGT activity by RTV	If the co-administration with bupropion is judged unavoidable, this should be done under close clinical monitoring for bupropion efficacy, without exceeding the recommended dosage, despite the observed induction.
Loperamide 16 mg QD	Loperamide C_{max} ↓ 61% Loperamide AUC ↓ 51% Mechanism unknown Tipranavir C_{max} ↔ Tipranavir AUC ↔ Tipranavir C_{min} ↓ 26%	A pharmacodynamic interaction study in healthy volunteers demonstrated that administration of loperamide and Aptivus, co-administered with low dose ritonavir, does not cause any clinically relevant change in the respiratory response to carbon dioxide. The clinical relevance of the reduced loperamide plasma concentration is unknown.
Fluticasone propionate Interaction study performed only with ritonavir	In a clinical study where ritonavir 100 mg capsules bid were co-administered with 50 µg intranasal fluticasone propionate (4 times daily) for 7 days in healthy subjects, the fluticasone propionate plasma levels increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86% (90% confidence interval 82-89%). Greater effects may be expected	Concomitant administration of Aptivus, co-administered with low dose ritonavir, and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4). A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a

	when fluticasone propionate is inhaled. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate; this could also occur with other corticosteroids metabolised via the P450 3A pathway e.g. budesonide. It is unknown whether the combination of tipranavir with ritonavir might cause a larger increase in fluticasone exposure.	glucocorticoid, which is not a substrate for CYP3A4 (e.g. beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may have to be performed over a longer period. The effects of high fluticasone systemic exposure on ritonavir plasma levels are as yet unknown.

4.6 Fertility, pregnancy and lactation

Contraception in males and females
Tipranavir adversely interacts with oral contraceptives. Therefore, an alternative, effective, safe method of contraception should be used during treatment (see section 4.5).

Pregnancy
There are no adequate data from the use of tipranavir in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Tipranavir should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breastfeeding
Consistent with the recommendation that HIV-infected mothers should not breast-feed their infants under any circumstances to avoid risking postnatal transmission of HIV, mothers should discontinue breast-feeding if they are receiving Aptivus.

Fertility
Clinical data on fertility are not available for tipranavir. Preclinical studies performed with tipranavir showed no adverse effect on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Dizziness, somnolence, and fatigue have been reported in some patients; therefore, caution should be recommended when driving a car or operating machinery. If patients experience fatigue, dizziness, or somnolence they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile
Amongst the most common adverse reactions reported for Aptivus were gastrointestinal complaints such as diarrhoea and nausea as well as hyperlipidaemia. The most serious adverse reactions include hepatic impairment and liver toxicity. Intracranial haemorrhage (ICH) was only observed in post marketing experience (see section 4.4).

Aptivus co-administered with low dose ritonavir, has been associated with reports of significant liver toxicity. In Phase III RESIST trials, the frequency of transaminase elevations was significantly increased in the tipranavir with ritonavir arm compared to the comparator arm. Close monitoring is therefore needed in patients treated with Aptivus, co-administered with low dose ritonavir (see section 4.4).

Limited data are currently available for the use of Aptivus, co-administered with low dose ritonavir, in patients co-infected with hepatitis B or C. Aptivus should therefore be used with caution in patients co-infected with hepatitis B or C. Aptivus should be used in this patient population only if the potential benefit outweighs the potential risk, and with increased clinical and laboratory monitoring.

Tabulated summary of adverse reactions

Assessment of adverse reactions from HIV-1 clinical study data is based on experience in all Phase II and III trials in adults treated with the 500 mg tipranavir with 200 mg ritonavir dose twice daily (n=1397) and are listed below by system organ class and frequency according to the following categories:

Very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000)

Tabulated summary of adverse reactions associated with Aptivus based on clinical studies and post-marketing experience:

Blood and lymphatic system disorders	
uncommon	neutropenia, anaemia, thrombocytopenia
Immune system disorders	
uncommon	hypersensitivity
Metabolism and nutrition disorders	
common	hypertriglyceridaemia, hyperlipidaemia
uncommon	anorexia, decreased appetite, weight decreased, hyperamylasaemia, hypercholesterolaemia, diabetes mellitus, hyperglycaemia
rare	dehydration, facial wasting
Psychiatric disorders	
uncommon	insomnia, sleep disorder
Nervous system disorders	
common	headache
uncommon	dizziness, neuropathy peripheral, somnolence
rare	intracranial haemorrhage*
Respiratory, thoracic and mediastinal disorders	
uncommon	dyspnoea
Gastrointestinal disorders	
very common	diarrhoea, nausea
common	vomiting, flatulence, abdominal pain, abdominal distension, dyspepsia
uncommon	gastrooesophageal reflux disease, pancreatitis
rare	lipase increased
Hepatobiliary disorders	
uncommon	hepatic enzyme increased (ALAT, ASAT), cytolytic hepatitis, liver function test abnormal (ALAT, ASAT), hepatitis toxic

rare	hepatic failure (including fatal outcome), hepatitis, hepatic steatosis, hyperbilirubinaemia
Skin and subcutaneous tissue disorders	
common	rash
uncommon	pruritus, lipohypertrophy, exanthem, lipoatrophy, lipodystrophy acquired
Musculoskeletal and connective tissue disorders	
uncommon	myalgia, muscle spasms
Renal and urinary disorders	
uncommon	renal failure
General disorders and administration site conditions	
common	fatigue
uncommon	pyrexia, influenza like illness, malaise

***** see section Description of selected adverse reactions "Bleeding" for source of information

Description of selected adverse reactions

The following clinical safety features (hepatotoxicity, hyperlipidaemia, bleeding events, rash) were seen at higher frequency among tipranavir with ritonavir treated patients when compared with the comparator arm treated patients in the RESIST trials, or have been observed with tipranavir with ritonavir administration. The clinical significance of these observations has not been fully explored.

Hepatotoxicity

After 48 weeks of follow-up, the frequency of Grade 3 or 4 ALAT and/or ASAT abnormalities was higher in tipranavir with ritonavir patients compared with comparator arm patients (10% and 3.4%, respectively). Multivariate analyses showed that baseline ALAT or ASAT above DAIDS Grade 1 and co-infection with hepatitis B or C were risk factors for these elevations. Most patients were able to continue treatment with tipranavir with ritonavir.

Hyperlipidaemia

Grade 3 or 4 elevations of triglycerides occurred more frequently in the tipranavir with ritonavir arm compared with the comparator arm. At 48 weeks these rates were 25.2% of patients in the tipranavir with ritonavir arm and 15.6% in the comparator arm.

Bleeding

This adverse reaction was identified through post-marketing surveillance but not observed in randomised controlled clinical trials (n=6300).

RESIST participants receiving tipranavir with ritonavir tended to have an increased risk of bleeding; at 24 weeks the relative risk was 1.98 (95% CI=1.03, 3.80). At 48-weeks the relative risk decreased to 1.27 (95% CI=0.76, 2.12). There was no pattern for the bleeding events and no difference between treatment groups in coagulation parameters. The significance of this finding is being further monitored.

Fatal and non-fatal intracranial haemorrhage (ICH) have been reported in patients receiving tipranavir, many of whom had other medical conditions or were receiving concomitant medicinal products that may have caused or contributed to these events. However, in some cases the role of tipranavir cannot be excluded. No pattern of abnormal haematological or coagulation parameters has been observed in patients in general, or preceding the development of ICH. Therefore, routine measurement of coagulation parameters is not currently indicated in the management of patients on Aptivus.

An increased risk of ICH has previously been observed in patients with advanced HIV disease/AIDS such as those treated in the Aptivus clinical trials.

Rash
An interaction study in women between tipranavir, co-administered with low dose ritonavir, and ethinyl oestradiol/norethindrone demonstrated a high frequency of non-serious rash. In the RESIST trials, the risk of rash was similar between tipranavir with ritonavir and comparator arms (16.3% vs. 12.5%, respectively; see section 4.4). No cases of Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis have been reported in the clinical development programme of tipranavir.

Laboratory abnormalities
Frequencies of marked clinical laboratory abnormalities (Grade 3 or 4) reported in at least 2% of patients in the tipranavir with ritonavir arms in the phase III clinical studies (RESIST-1 and RESIST-2) after 48-weeks were increased ASAT (6.1%), increased ALAT (9.7%), increased amylase (6.0%), increased cholesterol (4.2%), increased triglycerides (24.9%), and decreased white blood cell count (5.7%).

Combination antiretroviral therapy, including regimens containing a protease inhibitor, is associated with redistribution of body fat in some patients, including loss of peripheral subcutaneous fat, increased intra-abdominal fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump). Protease inhibitors are also associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance and hyperglycaemia.

Increased CPK, myalgia, myositis and, rarely, rhabdomyolysis, have been reported with protease inhibitors, particularly in combination with nucleoside reverse transcriptase inhibitors.

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

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

Paediatric population
In an open-label, dose-finding study of tipranavir plus ritonavir (Trial 1182.14), 62 children aged 2 to 12 years received Aptivus oral solution. In general, adverse reactions were similar to those seen in adults, with the exception of vomiting, rash and pyrexia which were reported more frequently in children than in adults. The most frequently reported moderate or severe adverse reactions in the 48 week analyses are noted below.

Most frequently reported moderate or severe adverse reactions in paediatric patients age 2 to < 12 years (reported in 2 or more children, Trial 1182.14, 48 weeks analyses, Full Analysis Set).

Total patients treated (N)	**62**
Events [N(%)]	
Diarrhoea	4 (6.5)
Vomiting	3 (4.8)
Nausea	3 (4.8)
Abdominal pain[1]	3 (4.8)
Pyrexia	4 (6.5)
Rash[2]	4 (6.5)
gamma GT increased	4 (6.5)
ALAT increased	2 (3.2)
Anaemia	2 (3.2)

[1] Includes abdominal pain (N=1), dysphagia (N=1) and epigastric discomfort (N=1).

[2] Rash consists of one or more of the preferred terms of rash, drug eruption, rash macular, rash papular, erythema, rash maculo-papular, rash pruritic, and urticaria.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Human experience with tipranavir overdose is very limited. No specific signs and symptoms of overdose are known. Generally, an increased frequency and higher severity of adverse reactions may result from overdose.

There is no known antidote for tipranavir overdose. Treatment of overdose should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. If indicated, elimination of unabsorbed tipranavir should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed substance. Since tipranavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, protease inhibitors, ATC code: J05AE09

Mechanism of action
The human immunodeficiency virus (HIV-1) encodes an aspartyl protease that is essential for the cleavage and maturation of viral protein precursors. Tipranavir is a non-peptidic inhibitor of the HIV-1 protease that inhibits viral replication by preventing the maturation of viral particles.

Antiviral activity *in vitro*
Tipranavir inhibits the replication of laboratory strains of HIV-1 and clinical isolates in acute models of T-cell infection, with 50% and 90% effective concentrations (EC_{50} and EC_{90}) ranging from 0.03 to 0.07 µM (18-42 ng/ml) and 0.07 to 0.18 µM (42-108 ng/ml), respectively. Tipranavir demonstrates antiviral activity *in vitro* against a broad panel of HIV-1 group M non-clade B isolates (A, C, D, F, G, H, CRF01 AE, CRF02 AG, CRF12 BF). Group O and HIV-2 isolates have reduced susceptibility *in vitro* to tipranavir with EC_{50} values ranging from 0.164-1 µM and 0.233-0.522 µM, respectively. Protein binding studies have shown that the antiviral activity of tipranavir decreases on average 3.75-fold in conditions where human serum is present.

Resistance
The development of resistance to tipranavir *in vitro* is slow and complex. In one particular *in vitro* resistance experiment, an HIV-1 isolate that was 87-fold resistant to tipranavir was selected after 9 months, and contained 10 mutations in the protease: L10F, I13V, V32I, L33F, M36I, K45I, I54V/T, A71V, V82L, I84V as well as a mutation in the gag polyprotein CA/P2 cleavage site. Reverse genetic experiments showed that the presence of 6 mutations in the protease (I13V, V32I, L33F, K45I, V82L, I84V) was required to confer > 10-fold resistance to tipranavir while the full 10-mutation genotype conferred 69-fold resistance to tipranavir. *In vitro*, there is an inverse correlation between the degree of resistance to tipranavir and the capacity of viruses to replicate. Recombinant viruses showing ≥ 3-fold resistance to tipranavir grow at less than 1% of the rate detected for wild type HIV-1 in the same conditions. Tipranavir resistant viruses which emerge *in vitro* from wild-type HIV-1 show decreased susceptibility to the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir and ritonavir but remain sensitive to saquinavir.

Through a series of multiple stepwise regression analyses of baseline and on-treatment genotypes from all clinical studies, 16 amino acids have been associated with reduced tipranavir susceptibility and/or reduced 48-week viral load response: 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D and 84V. Clinical isolates that exhibited a ≥ 10-fold decrease in tipranavir susceptibility harboured 8 or more tipranavir-associated mutations. In Phase II and III clinical trials, 276 patients with on-treatment genotypes have demonstrated that the predominant emerging mutations with tipranavir treatment are L33F/I/V, V82T/L and I84V. Combination of all three of these is usually required for reduced susceptibility. Mutations at position 82 occur via two pathways: one from pre-existing mutation 82A selecting to 82T, the other from wild type 82V selecting to 82L.

Cross-resistance
Tipranavir maintains significant antiviral activity (< 4-fold resistance) against the majority of HIV-1 clinical isolates showing post-treatment decreased susceptibility to the currently approved protease inhibitors: amprenavir, atazanavir, indinavir, lopinavir, ritonavir, nelfinavir and saquinavir. Greater than 10-fold resistance to tipranavir is uncommon (< 2.5% of tested isolates) in viruses obtained from highly treatment experienced patients who have received multiple peptidic protease inhibitors.

ECG evaluation
The effect of tipranavir with low dose of ritonavir on the QTcF interval was measured in a study in which 81 healthy subjects received 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.

Clinical pharmacodynamic data
This indication is based on the results of one phase II study investigating pharmacokinetics, safety and efficacy of Aptivus oral solution in mostly treatment-experienced children aged 2 to 12 years.

The following clinical data is derived from analyses of 48-week data from ongoing studies (RESIST-1 and RESIST-2) measuring effects on plasma HIV RNA levels and CD4 cell counts. RESIST-1 and RESIST-2 are ongoing, randomised, open-label, multicentre studies in HIV-positive, triple-class experienced patients, evaluating treatment with tipranavir 500 mg co-administered with low dose ritonavir 200 mg (twice daily) plus an optimised background regimen (OBR) individually defined for each patient based on genotypic resistance testing and patient history. The comparator regimen included a ritonavir-boosted PI (also individually defined) plus an OBR. The ritonavir-boosted PI was chosen from among saquinavir, amprenavir, indinavir or lopinavir/ritonavir.

All patients had received at least two PI-based antiretroviral regimens and were failing a PI-based regimen at the time of study entry. At least one primary protease gene mutation from among 30N, 46I, 46L, 48V, 50V, 82A, 82F, 82L, 82T, 84V or 90M had to be present at baseline, with not more than two mutations on codons 33, 82, 84 or 90.

After Week 8, patients in the comparator arm who met the protocol defined criteria of initial lack of virologic response had the option of discontinuing treatment and switching over to tipranavir with ritonavir in a separate roll-over study.

The 1483 patients included in the primary analysis had a median age of 43 years (range 17-80), were 86% male, 75% white, 13% black and 1% Asian. In the tipranavir and comparator arms median baseline CD4 cell counts were 158 and 166 cells/mm^3, respectively, (ranges 1-1893 and 1-1184 cells/mm^3); median baseline plasma HIV-1 RNA was 4.79 and 4.80 $\log_{10}$ copies/ml, respectively (ranges 2.34-6.52 and 2.01-6.76 $\log_{10}$ copies/ml).

Patients had prior exposure to a median of 6 NRTIs, 1 NNRTI, and 4 PIs. In both studies, a total of 67% patient viruses were resistant and 22% were possibly resistant to the pre-selected comparator PIs. A total of 10% of patients had previously used enfuvirtide. Patients had baseline HIV-1 isolates with a

median of 16 HIV-1 protease gene mutations, including a median of 3 primary protease gene mutations D30N, L33F/I, V46I/L, G48V, I50V, V82A/F/T/L, I84V, and L90M. With respect to mutations on codons 33, 82, 84 and 90 approximately 4% had no mutations, 24% had mutations at codons 82 (less than 1% of patients had the mutation V82L) and 90, 18% had mutations at codons 84 and 90 and 53% had at least one key mutation at codon 90. One patient in the tipranavir arm had four mutations. In addition the majority of participants had mutations associated with both NRTI and NNRTI resistance. Baseline phenotypic susceptibility was evaluated in 454 baseline patient samples. There was an average decrease in susceptibility of 2-fold wild type (WT) for tipranavir, 12-fold WT for amprenavir, 55-fold WT for atazanavir, 41-fold WT for indinavir, 87-fold WT for lopinavir, 41-fold WT for nelfinavir, 195-fold WT for ritonavir, and 20-fold WT for saquinavir.

Combined 48-week treatment response (composite endpoint defined as patients with a confirmed ≥1 log RNA drop from baseline and without evidence of treatment failure) for both studies was 34% in the tipranavir with ritonavir arm and 15% in the comparator arm. Treatment response is presented for the overall population (displayed by enfuvirtide use), and detailed by PI strata for the subgroup of patients with genotypically resistant strains in the Table below.

Treatment response* at week 48 (pooled studies RESIST-1 and RESIST-2 in treatment-experienced patients)

RESIST study	Tipranavir /RTV		CPI/RTV**		p-value
	n (%)	N	n (%)	N	
Overall population					
FAS	255 (34.2)	746	114 (15.5)	737	<0.0001
PP	171 (37.7)	454	74 (17.1)	432	<0.0001
- with ENF (FAS)	85 (50.0)	170	28 (20.7)	135	<0.0001
- without ENF (FAS)	170 (29.5)	576	86 (14.3)	602	<0.0001
Genotypically Resistant					
LPV/rtv					
FAS	66 (28.9)	228	23 (9.5)	242	<0.0001
PP	47 (32.2)	146	13 (9.1)	143	<0.0001
APV/rtv					
FAS	50 (33.3)	150	22 (14.9)	148	<0.0001
PP	38 (39.2)	97	17 (18.3)	93	0.0010
SQV/rtv					
FAS	22 (30.6)	72	5 (7.0)	71	<0.0001
PP	11 (28.2)	39	2 (5.7)	35	0.0650
IDV/rtv					
FAS	6 (46.2)	13	1 (5.3)	19	0.0026
PP	3 (50.0)	6	1 (7.1)	14	0.0650

* Composite endpoint defined as patients with a confirmed 1 log RNA drop from baseline and without evidence of treatment failure

** Comparator PI/RTV: LPV/r 400 mg/100 mg twice daily (n=358), IDV/r 800 mg/100 mg twice daily (n=23), SQV/r 1000 mg/100 mg twice daily or 800 mg/200 mg twice daily (n=162), APV/r 600 mg/100 mg twice daily (n=194)

ENF Enfuvirtide; FAS Full Analysis Set; PP Per Protocol; APV/rtv Amprenavir/ritonavir; IDV/rtv Indinavir/ritonavir; LPV/rtv Lopinavir/ritonavir; SQV/rtv Saquinavir/ritonavir

Combined 48-week median time to treatment failure for both studies was 115 days in the tipranavir with ritonavir arm and 0 days in the comparator arm (no treatment response was imputed to day 0).

Through 48 weeks of treatment, the proportion of patients in the tipranavir with ritonavir arm compared to the comparator PI/ritonavir arm with HIV-1 RNA < 400 copies/ml was 30% and 14% respectively, and with HIV-1 RNA < 50 copies/ml was 23% and 10% respectively. Among all randomised and treated patients, the median change from baseline in HIV-1 RNA at the last

measurement up to Week 48 was -0.64 log_{10} copies/ml in patients receiving tipranavir with ritonavir versus -0.22 log_{10} copies/ml in the comparator PI/ritonavir arm.

Among all randomised and treated patients, the median change from baseline in CD4+ cell count at the last measurement up to Week 48 was +23 cells/mm^3 in patients receiving tipranavir with ritonavir (N=740) versus +4 cells/mm^3 in the comparator PI/ritonavir (N=727) arm.

The superiority of tipranavir co-administered with low dose ritonavir over the comparator protease inhibitor/ritonavir arm was observed for all efficacy parameters at week 48. It has not been shown that tipranavir is superior to these boosted comparator protease inhibitors in patients harbouring strains susceptible to these protease inhibitors. RESIST data also demonstrate that tipranavir co-administered with low dose ritonavir exhibits a better treatment response at 48 weeks when the OBR contains genotypically available antiretroviral agents (e.g. enfuvirtide).

At present there are no results from controlled trials evaluating the effect of tipranavir on clinical progression of HIV.

Paediatric population

HIV-positive, paediatric patients, aged 2 through 18 years, were studied in a randomized, open-label, multicenter study (trial 1182.14). Patients were required to have a baseline HIV-1 RNA concentration of at least 1500 copies/ml, were stratified by age (2 to < 6 years, 6 to < 12 years and 12 to 18 years) and randomized to receive one of two tipranavir with ritonavir dose regimens: 375 mg/m^2/150 mg/m^2 dose, compared to the 290 mg/m^2/115 mg/m^2 dose, plus background therapy of at least two non-protease inhibitor antiretroviral medicinal products, optimized using baseline genotypic resistance testing. All patients initially received Aptivus oral solution. Paediatric patients who were 12 years or older and received the maximum dose of 500 mg/200 mg twice daily could change to Aptivus capsules from study day 28. The trial evaluated pharmacokinetics, safety and tolerability, as well as virologic and immunologic responses through 48 weeks.

The available clinical data do not support the use of Aptivus oral solution in adolescents or adults. Compared to the capsules, tipranavir exposure is higher when administering the same dose as oral solution (see section 5.2). Due to this and to the high vitamin E content of the oral solution, the risk of adverse reactions (type, frequency and/or severity) may be higher than with the capsule formulation. In patients less than 12 years of age, however, the oral solution is the only available option for treatment with tipranavir, as no data are available on the efficacy and safety of Aptivus capsules in children less than 12 years of age. Since Aptivus capsules and oral solution are not bioequivalent, results obtained with the oral solution cannot be extrapolated to the capsules (see also section 5.2). Moreover, in patients with a body surface area of less than 1.33 m² appropriate dose adjustments cannot be achieved with the capsule formulation. These factors lead to the conclusion that the benefits outweigh the risks of Aptivus oral solution only in children between 2 and 12 years of age without any other therapeutic option (see section 4.1).

The baseline characteristics and the key efficacy results at 48 weeks for the paediatric patients receiving Aptivus oral solution are displayed in the tables below.

Baseline characteristics for patients 2 - <12 years treated with Aptivus oral solution

Variable		**Value**
Number of Patients		62
Age-Median (years)		8.1
Gender	% Male	59.7%
Race	% White	71.0%
	% Black	25.8%
	% Asian	3.2%
Baseline HIV-1 RNA (log_{10} copies/ml)	Median (Min – Max)	4.8 (3.3 – 6.0)

	% with VL > 100,000 copies/ml	37.1%
Baseline CD4+ (cells/mm^3)	Median (Min – Max)	600 (24 – 2578)
	% ≤ 200	15.5%
Baseline % CD4+ cells	Median (Min – Max)	21.9% (1.5% – 44.0%)
Previous ADI*	% with Category C	48.4%
Treatment history	% with any ARV	96.8%
	Median # previous NRTIs	4
	Median # previous NNRTIs	1
	Median # previous PIs	1

* AIDS defining illness

Key efficacy results at 48 weeks for patients 2 - <12 years treated with Aptivus oral solution

Endpoint	**Result**
Number of patients	62
Primary efficacy endpoint: % with VL < 400	50.0%
Median change from baseline in log10 HIV-1 RNA (copies/ml)	-2.06
Median change from baseline in CD4+ cell count (cells/mm3)	167
Median change from baseline in % CD4+ cells	5%

Analyses of tipranavir resistance in treatment experienced patients
Tipranavir with ritonavir response rates in the RESIST studies were assessed by baseline tipranavir genotype and phenotype. Relationships between baseline phenotypic susceptibility to tipranavir, primary PI mutations, protease mutations at codons 33, 82, 84 and 90, tipranavir resistance-associated mutations, and response to tipranavir with ritonavir therapy were assessed.

Of note, patients in the RESIST studies had a specific mutational pattern at baseline of at least one primary protease gene mutation among codons 30N, 46I, 46L, 48V, 50V, 82A, 82F, 82L, 82T, 84V or 90M, and no more than two mutations on codons 33, 82, 84 or 90.

The following observations were made:

– *Primary PI mutations*
Analyses were conducted to assess virological outcome by the number of primary PI mutations (any change at protease codons 30, 32, 36, 46, 47, 48, 50, 53, 54, 82, 84, 88 and 90) present at baseline. Response rates were higher in tipranavir with ritonavir patients than comparator PI boosted with ritonavir in new enfuvirtide patients, or patients without new enfuvirtide. However, without new enfuvirtide some patients began to lose antiviral activity between weeks 4 and 8.

– *Mutations at protease codons 33, 82, 84 and 90*
A reduced virological response was observed in patients with viral strains harbouring two or more mutations at HIV protease codons 33, 82, 84 or 90, and not receiving new enfuvirtide.

– *Tipranavir resistance-associated mutations*
Virological response to tipranavir with ritonavir therapy has been evaluated using a tipranavir-associated mutation score based on baseline genotype in RESIST-1 and RESIST-2 patients. This score

(counting the 16 amino acids that have been associated with reduced tipranavir susceptibility and/or reduced viral load response: 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D and 84V) was applied to baseline viral protease sequences. A correlation between the tipranavir mutation score and response to tipranavir with ritonavir therapy at week 48 has been established.

This score has been determined from the selected RESIST patient population having specific mutation inclusion criteria and therefore extrapolation to a wider population mandates caution.

At 48-weeks, a higher proportion of patients receiving tipranavir with ritonavir achieved a treatment response in comparison to the comparator protease inhibitor/ritonavir for nearly all of the possible combinations of genotypic resistance mutations (see table below).

Proportion of patients achieving treatment response at Week 48 (confirmed ≥1 $\log_{10}$ copies/ml decrease in viral load compared to baseline), according to tipranavir baseline mutation score and enfuvirtide use in RESIST patients

	New ENF	No New ENF*
Number of TPV Score Mutations**	TPV/r	TPV/r
0,1	73%	53%
2	61%	33%
3	75%	27%
4	59%	23%
≥ 5	47%	13%
All patients	61%	29%

* Includes patients who did not receive ENF and those who were previously treated with and continued ENF
**Mutations in HIV protease at positions L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, 58E, H69K, T74P, V82L/T, N83D or I84V
ENF Enfuvirtide; TPV/r Tipranavir with ritonavir

Sustained HIV-1 RNA decreases up to week 48 were mainly observed in patients who received tipranavir with ritonavir and new enfuvirtide. If patients did not receive tipranavir with ritonavir with new enfuvirtide, diminished treatment responses at week 48 were observed, relative to new enfuvirtide use (see Table below).

Mean decrease in viral load from baseline to week 48, according to tipranavir baseline mutation score and enfuvirtide use in RESIST patients

	New ENF	No New ENF*
Number of TPV Score Mutations**	TPV/r	TPV/r
0, 1	-2.3	-1.6
2	-2.1	-1.1
3	-2.4	-0.9
4	-1.7	-0.8
≥ 5	-1.9	-0.6
All patients	-2.0	-1.0

* Includes patients who did not receive ENF and those who were previously treated with and continued ENF

** Mutations in HIV protease at positions L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, 58E, H69K, T74P, V82L/T, N83D or I84V
ENF Enfuvirtide; TPV/r Tipranavir with ritonavir

– *Tipranavir phenotypic resistance*
Increasing baseline phenotypic fold change to tipranavir in isolates is correlated to decreasing virological response. Isolates with baseline fold change of >0 to 3 are considered susceptible; isolates with >3 to 10 fold changes have decreased susceptibility; isolates with >10 fold changes are resistant.

Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change with additional data, and it is recommended to always consult current interpretation systems for analysing resistance test results.

5.2 Pharmacokinetic properties

In order to achieve effective tipranavir plasma concentrations and a twice daily dosing regimen, coadministration of tipranavir with low dose ritonavir twice daily is essential (see section 4.2). Ritonavir acts by inhibiting hepatic cytochrome P450 CYP3A, the intestinal P-glycoprotein (P-gp) efflux pump and possibly intestinal cytochrome P450 CYP3A as well. As demonstrated in a dose-ranging evaluation in 113 HIV-negative healthy male and female volunteers, ritonavir increases AUC_{0-12h}, C_{max} and C_{min} and decreases the clearance of tipranavir. 500 mg tipranavir co-administered with low dose ritonavir (200 mg; twice daily) was associated with a 29-fold increase in the geometric mean morning steady-state trough plasma concentrations compared to tipranavir 500 mg twice daily without ritonavir.

Absorption
Absorption of tipranavir in humans is limited, though no absolute quantification of absorption is available. Tipranavir is a P-gp substrate, a weak P-gp inhibitor and appears to be a potent P-gp inducer as well. Data suggest that, although ritonavir is a P-gp inhibitor, the net effect of Aptivus, co-administered with low dose ritonavir, at the proposed dose regimen at steady-state, is P-gp induction. Peak plasma concentrations are reached within 1 to 5 hours after dose administration depending upon the dosage used. With repeated dosing, tipranavir plasma concentrations are lower than predicted from single dose data, presumably due to hepatic enzyme induction. Steady-state is attained in most subjects after 7 days of dosing. Tipranavir, co-administered with low dose ritonavir, exhibits linear pharmacokinetics at steady state.

Dosing with Aptivus capsules 500 mg twice daily concomitant with 200 mg ritonavir twice daily for 2 to 4 weeks and without meal restriction produced a mean tipranavir peak plasma concentration (C_{max}) of 94.8 ± 22.8 μM for female patients (n=14) and 77.6 ± 16.6 μM for male patients (n=106), occurring approximately 3 hours after administration. The mean steady-state trough concentration prior to the morning dose was 41.6 ± 24.3 μM for female patients and 35.6 ± 16.7 μM for male patients. Tipranavir AUC over a 12 hour dosing interval averaged 851 ± 309 μM•h (CL=1.15 l/h) for female patients and 710 ± 207 μM•h (CL=1.27 l/h) for male patients. The mean half-life was 5.5 (females) or 6.0 hours (males).

Effects of food on oral absorption
Food improves the tolerability of tipranavir with ritonavir. Therefore Aptivus, co-administered with low dose ritonavir, should be given with food.

Absorption of tipranavir, co-administered with low dose ritonavir, is reduced in the presence of antacids (see section 4.5).

Distribution
Tipranavir is extensively bound to plasma proteins (>99.9%). From clinical samples of healthy volunteers and HIV-1 positive subjects who received tipranavir without ritonavir the mean fraction of tipranavir unbound in plasma was similar in both populations (healthy volunteers 0.015% ± 0.006%; HIV-positive subjects 0.019% ± 0.076%). Total plasma tipranavir concentrations for these samples

ranged from 9 to 82 μM. The unbound fraction of tipranavir appeared to be independent of total concentration over this concentration range.

No studies have been conducted to determine the distribution of tipranavir into human cerebrospinal fluid or semen.

Biotransformation
In vitro metabolism studies with human liver microsomes indicated that CYP3A4 is the predominant CYP isoform involved in tipranavir metabolism.

The oral clearance of tipranavir decreased after the addition of ritonavir which may represent diminished first-pass clearance of the substance at the gastrointestinal tract as well as the liver.

The metabolism of tipranavir in the presence of low dose ritonavir is minimal. In a ^{14}C-tipranavir human study (500 mg ^{14}C-tipranavir with 200 mg ritonavir, twice daily), unchanged tipranavir was predominant and accounted for 98.4% or greater of the total plasma radioactivity circulating at 3, 8, or 12 hours after dosing. Only a few metabolites were found in plasma, and all were at trace levels (0.2% or less of the plasma radioactivity). In faeces, unchanged tipranavir represented the majority of faecal radioactivity (79.9% of faecal radioactivity). The most abundant faecal metabolite, at 4.9% of faecal radioactivity (3.2% of dose), was a hydroxyl metabolite of tipranavir. In urine, unchanged tipranavir was found in trace amounts (0.5% of urine radioactivity). The most abundant urinary metabolite, at 11.0% of urine radioactivity (0.5% of dose) was a glucuronide conjugate of tipranavir.

Elimination
Administration of ^{14}C-tipranavir to subjects (n = 8) that received 500 mg tipranavir with 200 mg ritonavir twice daily dosed to steady-state demonstrated that most radioactivity (median 82.3%) was excreted in faeces, while only a median of 4.4% of the radioactive dose administered was recovered in urine. In addition, most radioactivity (56%) was excreted between 24 and 96 hours after dosing. The effective mean elimination half-life of tipranavir with ritonavir in healthy volunteers (n = 67) and HIV-infected adult patients (n = 120) was approximately 4.8 and 6.0 hours, respectively, at steady state following a dose of 500 mg/200 mg twice daily with a light meal.

Special populations
Although data available at this stage are currently limited to allow a definitive analysis, they suggest that the pharmacokinetic profile is unchanged in older people and comparable between races. By contrast, evaluation of the steady-state plasma tipranavir trough concentrations at 10-14 h after dosing from the RESIST-1 and RESIST-2 studies demonstrate that females generally had higher tipranavir concentrations than males. After four weeks of Aptivus 500 mg with 200 mg ritonavir (twice daily) the median plasma trough concentration of tipranavir was 43.9 μM for females and 31.1 μM for males. This difference in concentrations does not warrant a dose adjustment.

Renal impairment
Tipranavir pharmacokinetics have not been studied in patients with renal impairment. However, since the renal clearance of tipranavir is negligible, a decrease in total body clearance is not expected in patients with renal impairment.

Hepatic impairment
In a study comparing 9 patients with mild (Child-Pugh A) hepatic impairment to 9 controls, the single and multiple dose exposure of tipranavir and ritonavir were increased in patients with hepatic impairment but still within the range observed in clinical studies. No dosing adjustment is required in patients with mild hepatic impairment but patients should be closely monitored (see sections 4.2 and 4.4).

The influence of moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment on the multiple dose pharmacokinetics of either tipranavir or ritonavir has so far not been investigated. Tipranavir is contraindicated in moderate or severe hepatic impairment (see sections 4.2 and 4.3).

Paediatric population
The oral solution has been shown to have greater bioavailability than the soft capsule formulation.

5.3 Preclinical safety data

Animal toxicology studies have been conducted with tipranavir alone, in mice, rats and dogs, and co-administered with ritonavir (3.75:1 w/w ratio) in rats and dogs. Studies with co-administration of tipranavir and ritonavir did not reveal any additional toxicological effects when compared to those seen in the tipranavir single agent toxicological studies.

The predominant effects of repeated administration of tipranavir across all species toxicologically tested were on the gastrointestinal tract (emesis, soft stool, diarrhoea) and the liver (hypertrophy). The effects were reversible with termination of treatment. Additional changes included bleeding in rats at high doses (rodents specific). Bleeding observed in rats was associated with prolonged prothrombin time (PT), activated partial thromboplastin time (APTT) and a decrease in some vitamin K dependent factors. The co-administration of tipranavir with vitamin E in the form of TPGS (d-alphatocopherol polyethylene glycol 1000 succinate) from 2,322 IU/m² upwards in rats resulted in a significant increase in effects on coagulation parameters, bleeding events and death. In preclinical studies of tipranavir in dogs, an effect on coagulation parameters was not seen. Co-administration of tipranavir and vitamin E has not been studied in dogs.

The majority of the effects in repeat-dose toxicity studies appeared at systemic exposure levels which are equivalent to or even below the human exposure levels at the recommended clinical dose.

In *in vitro* studies, tipranavir was found to inhibit platelet aggregation when using human platelets (see section 4.4) and thromboxane A2 binding in an in vitro cell model at levels consistent with exposure observed in patients receiving Aptivus with ritonavir. The clinical implications of these findings are not known.

In a study conducted in rats with tipranavir at systemic exposure levels (AUC) equivalent to human exposure at the recommended clinical dose, no adverse effects on mating or fertility were observed. At maternal doses producing systemic exposure levels similar to or below those at the recommended clinical dose, tipranavir did not produce teratogenic effects. At tipranavir exposures in rats at 0.8-fold human exposure at the clinical dose, foetal toxicity (decreased sternebrae ossification and body weights) was observed. In pre- and post-natal development studies with tipranavir in rats, growth inhibition of pups was observed at maternally toxic doses approximating 0.8-fold human exposure.

Carcinogenicity studies of tipranavir in mice and rats revealed tumourigenic potential specific for these species, which are regarded as of no clinical relevance. Tipranavir showed no evidence of genetic toxicity in a battery of *in vitro* and *in vivo* tests.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol
Vitamin E polyethylene glycol succinate
Purified water
Propylene glycol
Mono/diglycerides of caprylic/capric acid
Sucralose
Butter mint (flavouring)
Butter toffee (flavouring)
Ascorbic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

In use storage: 60 days, after first opening of the bottle. It is advisable that the patient writes the date of opening the bottle on the label and/or carton.

6.4 Special precautions for storage

Do not store below 15°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

Amber glass bottle, with two-piece child-resistant closure (outer shell high density polyethylene (HDPE), inner shell polypropylene with a foamed low density polyethylene (LDPE)/HDPE liner). Each pack contains 1 bottle of 95 ml oral solution and is supplied with a clear polypropylene 5 ml oral syringe, polypropylene syringe cap and clear LDPE bottle-syringe adapter.

6.6 Special precautions for disposal and other handling

Before taking Aptivus it should be checked that the oral solution is clear and whether there are crystals or other particles at the bottom of the bottle. A small amount of crystals may be observed in the bottle, which does not affect the potency or safety of the product. If observed, crystals are typically seen as a paper-thin layer on the bottom when the bottle is stored upright. Dosing by means of the measuring device remains accurate even when crystals are observed. If there is more than a thin layer of crystals at the bottom of the bottle or uncertainty about the amount of crystals observed, the bottle should be returned for a replacement as soon as possible. Until the bottle is exchanged the patient should continue to take the usual doses of the oral solution. Patients should be instructed to observe closely for crystals.

The exact dose should be measured using the supplied measuring syringe and adapter, as follows:

1. Open the bottle by pressing down on the cap and turning in an anti-clockwise direction.
2. Remove the syringe cap covering the tip of the oral syringe (the cap will not be attached if this is the first time the oral syringe has been used) and insert the oral syringe into the adapter located in the neck of the bottle. Make sure the oral syringe is tightly inserted.
3. Turn the bottle upside down and gently withdraw the required amount of Aptivus oral solution.
4. Administer Aptivus oral solution immediately. The maximum volume which can be withdrawn at one time is 5 ml (equivalent to 500 mg tipranavir), which is the maximum single dose for a child with BSA > 1.33 m^2.
5. After use of the oral syringe, reapply the syringe cap.

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/315/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 October 2005
Date of latest renewal: 05 October 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Boehringer Ingelheim Pharma GmbH & Co. KG, Binger Strasse 173, D-55216 Ingelheim am Rhein, Germany.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted

- At the request of the European Medicines Agency
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX/OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Aptivus 250 mg soft capsules
tipranavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each soft capsule contains 250 mg tipranavir

3. LIST OF EXCIPIENTS

Contains macrogolglycerol ricinoleate, sorbitol and ethanol (see package leaflet for further information)

4. PHARMACEUTICAL FORM AND CONTENTS

120 soft capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
In use storage: 60 days (below 25°C) after first opening of the bottle.
Date of first opening of the bottle:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/315/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Aptivus 250 mg

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE/IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Aptivus 250 mg soft capsules
tipranavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each soft capsule contains 250 mg tipranavir

3. LIST OF EXCIPIENTS

Contains macrogolglycerol ricinoleate, sorbitol and ethanol (see package leaflet for further information)

4. PHARMACEUTICAL FORM AND CONTENTS

120 soft capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
In use storage: 60 days (below 25°C) after first opening of the bottle.
Date of first opening of the bottle:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/315/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER

FOLDING BOX/OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Aptivus 100 mg/ml oral solution
tipranavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 mg tipranavir

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

95 ml oral solution (1 bottle)
Oral syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store below 15°C. Do not refrigerate or freeze
After first opening of the bottle, the product can be used for 60 days.
Date of first opening of the bottle:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/315/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Aptivus 100 mg/ml

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE/IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Aptivus 100 mg/ml oral solution
tipranavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 mg tipranavir

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

95 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store below 15°C. Do not refrigerate or freeze
After first opening of the bottle, the product can be used for 60 days.
Date of first opening:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/315/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Aptivus 250 mg soft capsules
tipranavir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

If Aptivus has been prescribed for your child, please note that all information in this leaflet is addressed to your child (in this case please read "your child" instead of "you").

1. What Aptivus is and what it is used for

Aptivus contains the active substance tipranavir. It belongs to a group of medicines called protease inhibitors and is used in the treatment of Human Immunodeficiency Virus (HIV) infection. It blocks an enzyme called protease that is involved in the reproduction of HIV. When the enzyme is blocked, the virus does not reproduce normally, slowing down the infection. You must take Aptivus together with:

- low dose ritonavir (this helps Aptivus to reach a high enough level in your blood)
- other HIV medicines. Your doctor, together with you, will decide which other medicines you should take. This will depend on, for example:
  - which other medicines you have already taken for HIV
  - which medicines your HIV is resistant to. If your HIV is resistant to some HIV medicines, this means that the medicine will not work so well, or will not work at all.

Aptivus is specifically used for the treatment of HIV which is resistant to most other protease inhibitors. Before starting treatment, your doctor will have taken blood samples to test the resistance of your HIV. These tests will have confirmed that the HIV in your blood is resistant to most other protease inhibitors. Aptivus treatment is therefore appropriate for you. You should not use Aptivus if you have never received antiretroviral therapy or have other antiretroviral options available.

Aptivus soft capsules are indicated for:
- adolescents 12 years of age or older
- adults

2. What you need to know before you take Aptivus

You must take Aptivus in combination with low dose ritonavir and other antiretroviral medicines. It is therefore important that you know about these medicines too. You should therefore carefully read the Package Leaflets of ritonavir and your other antiretroviral medicines. If you have any further questions about ritonavir or the other medicines you are prescribed, please ask your doctor or pharmacist.

Do not take Aptivus
- if you are allergic to tipranavir or any of the other ingredients of this medicine (listed in section 6)
- if you have moderate to severe liver problems. Your doctor will take a blood sample to test how well your liver is working (your liver function). Depending on your liver function you may have to delay or stop Aptivus treatment
- if you are currently taking products containing:
    - rifampicin (used to treat tuberculosis)
    - cisapride (used to treat stomach problems)
    - pimozide or sertindole (used to treat schizophrenia)
    - quetiapine (used to treat schizophrenia, bipolar disorder and major depressive disorder)
    - triazolam or oral midazolam (taken by mouth). These medicines are used to treat anxiety or sleep disorders
    - ergot derivatives (used to treat headaches)
    - astemizole or terfenadine (used to treat allergies or hay fever)
    - simvastatin or lovastatin (used to lower blood cholesterol)
    - amiodarone, bepridil, flecainide, propafenone or quinidine (used to treat heart disorders)
    - metoprolol (used to treat heart failure)
    - alfuzosin and sildenafil (when used to treat a rare blood vessel disorder characterized by increased pressure in the pulmonary artery)
    - colchicine (when used to treat gout flares in patients with kidney or liver disease).

Do not take products containing St John's wort (a herbal remedy for depression). This may stop Aptivus from working properly.

Warnings and precautions
Talk to your doctor or pharmacist before taking Aptivus.

Tell your doctor if you have:
- type A or B haemophilia
- diabetes
- liver disease.

If you have:
- high liver function test results
- hepatitis B or C infection

you are at increased risk of severe and potentially fatal liver damage while taking Aptivus. Your doctor will monitor your liver function by blood tests before and during Aptivus treatment. If you have liver disease or hepatitis, your doctor will decide if you need additional testing. You should inform your doctor as soon as possible if you notice the signs or symptoms of hepatitis:
- fever
- malaise (feeling generally unwell)
- nausea (upset stomach)
- vomiting
- abdominal pain
- tiredness
- jaundice (yellowing of the skin or the eyeballs)

Aptivus is not a cure for HIV infection:
You should know that you may continue to develop infections and other illnesses associated with HIV disease. You should therefore remain in regular contact with your doctor. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people.

Rash:
Mild to moderate rash, including:
- hives
- rash with flat or raised small red spots
- sensitivity to the sun

have been reported in approximately 1 in 10 patients receiving Aptivus. Some patients who developed rash also had:
- joint pain or stiffness
- throat tightness
- generalized itching

Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat.

Your doctor may decide to monitor your levels of blood lipids (fats) before and during Aptivus treatment.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection (for example fever, enlarged lymph nodes), please inform your doctor immediately.

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

Tell your doctor if you experience fainting or a sensation of abnormal heart beats. Aptivus in combination with low dose ritonavir may cause changes in your heart rhythm and the electrical activity of your heart. These changes may be seen on an ECG (electrocardiogram).

Bone problems: Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Children
Aptivus soft capsules should not be used by children under 12 years of age.

Older people
If you are older than 65 years your doctor will exercise caution when prescribing Aptivus soft capsules to you and will closely monitor your therapy. Tipranavir has been used in limited number of patients 65 years or older.

Other medicines and Aptivus
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

This is **very important**. If you take other medicines at the same time as Aptivus and ritonavir, this can strengthen or weaken the effect of the medicines. These effects are called interactions, and can lead to serious side effects, or prevent proper control of other conditions you may have.

Interactions with other HIV medicines:
- etravirine belongs to a class of HIV medicines called non-nucleoside reverse transcriptase inhibitors (NNRTIs). Taking Aptivus with etravirine is not recommended.

- abacavir and zidovudine. These belong to a class of HIV medicines called nucleoside reverse transcriptase inhibitors (NRTIs). Your doctor will only prescribe you abacavir and zidovudine if you are unable to take other NRTIs.

- didanosine: If you are taking didanosine enteric coated tablets, you should take them at least two hours before or after Aptivus.

- emtricitabine: If you are taking emtricitabine your kidney function should be checked before initiation of Aptivus.

- rilpivirine: If you are taking rilpivirine, your doctor will monitor you closely.

- Protease Inhibitors (PIs): Taking Aptivus may cause large decreases in the blood levels of other HIV protease inhibitors. For example the protease inhibitors amprenavir, atazanavir, lopinavir and saquinavir will be decreased.
  Taking Aptivus, with atazanavir, may cause the blood levels of Aptivus and ritonavir to increase a lot.
  Your doctor will carefully consider whether to treat you with combinations of Aptivus and protease inhibitors.

Other medicines with which Aptivus may interact include:
- oral contraceptives/hormone replacement therapy (HRT): If you are taking the contraceptive pill to prevent pregnancy you should use an additional or different type of contraception (e.g. barrier contraception like condoms). Generally, it is not recommended to take Aptivus, with ritonavir, together with oral contraceptives or hormone replacement therapy (HRT). You should check with your doctor if you do wish to continue taking oral contraceptives or HRT. If you use oral contraceptives or HRT you have an increased chance of developing a skin rash while taking Aptivus. If a rash occurs, it is usually mild to moderate. You should talk to your doctor as you may need to temporarily stop taking either Aptivus or your oral contraceptives or HRT
- carbamazepine, phenobarbital and phenytoin (used to treat epilepsy). These may decrease the effectiveness of Aptivus.
- sildenafil, vardenafil, tadalafil (medicines used to produce and maintain an erection). The effects of sildenafil and vardenafil are likely to be increased if you take them with Aptivus. You should not be prescribed tadalafil until you have been taking Aptivus for 7 days or more.
- omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole (proton pump inhibitors used to reduce the gastric acid production)
- metronidazole (used to treat infections)
- disulfiram (used to treat alcohol dependence)
- buprenorphine/naloxone (medicines used to treat severe pain)
- cyclosporin, tacrolimus, sirolimus (used to prevent organ rejection (to suppress the immune system))
- warfarin (used to treat and prevent thrombosis)
- digoxin (used to treat heart arrhythmias and heart failure)
- antifungal medications including fluconazole, itraconazole, ketoconazole or voriconazole

The following medicines are not recommended:
- fluticasone (used to treat asthma)
- atorvastatin (used to lower blood cholesterol)
- salmeterol (used to achieve long-term asthma control, bronchospasm prevention with COPD)
- bosentan (used to treat pulmonary artery hypertension)
- halofantrine or lumefantrine (used to treat malaria)
- tolterodine (used to treat overactive bladder (with symptoms of urinary frequency, urgency, or urge incontinence))
- boceprevir and telaprevir (used to treat hepatitis C)
- cobicistat and products containing cobicistat (used to increase effectiveness of HIV medicines).

Aptivus may lead to a loss of effectiveness of some medicines including:
- methadone, meperidine (pethidine), used as morphine substitutes

Your doctor may have to increase or decrease the dose of other medicines which you take together with Aptivus. Examples include:
- rifabutin and clarithromycin (antibiotics)
- theophylline (used to treat asthma)
- desipramine, trazodone and bupropion (used to treat depression; bupropion is also used for smoking cessation)
- midazolam (when given by injection); midazolam is a sedative used to treat anxiety and to help you sleep
- rosuvastatin or pravastatin (used to lower blood cholesterol)
- colchicine (used to treat gout flares with normal kidney and liver function).

If you take aluminium- and magnesium-based antacid (used to treat dyspepsia/gastrooesophageal reflux), the time interval between Aptivus and antacid should be at least two hours.

Tell your doctor if you receive medicines such as blood-thinning agents, or if you are taking vitamin E. Your doctor may wish to consider certain precautionary measures in such circumstances.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. It is not known whether Aptivus may be used safely during pregnancy. You must not breast-feed your baby because it is possible that the baby can become HIV-infected through the breast milk. See also Section 2, under “Oral contraceptives/hormone replacement therapy (HRT)”.
Aptivus contains very small amounts of alcohol (see *Aptivus capsules contain ethanol*).

Driving and using machines
Some of the side effects of Aptivus may affect your ability to drive or operate machinery (e.g. dizziness and sleepiness). If affected, you should not drive or operate machinery.

Aptivus capsules contain ethanol, macrogolglycerol ricinoleate and sorbitol (E420)
Aptivus contains 7 % ethanol (alcohol), i.e. up to 400 mg per daily dose, equivalent to 8 ml of beer, or less than 4 ml of wine. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.

Aptivus also contains macrogolglycerol ricinoleate which may cause stomach upset and diarrhoea.

This medicine contains sorbitol. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Aptivus

Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. You must take Aptivus together with ritonavir.

The recommended dose for an adult or an adolescent 12 years and above is:
- 500 mg (two 250 mg capsules) Aptivus together with
- 200 mg (two 100 mg capsules) ritonavir

twice per day with food.

Oral use.
Aptivus capsules should be taken with food.

Always take this medicine in combination with other antiretroviral medicines. You should follow the instructions for these medicines within the supplied Package Leaflets.

You should continue to take Aptivus for as long as your doctor tells you.

If you take more Aptivus than you should
Inform your doctor as soon as possible if you take more than the prescribed dose of Aptivus.

If you forget to take Aptivus
If you miss a dose of Aptivus or ritonavir by more than 5 hours, wait and then take the next dose of Aptivus and ritonavir at the regularly scheduled time. If you miss a dose of Aptivus and/or ritonavir by less than 5 hours, take your missed dose immediately. Then take your next dose of Aptivus and ritonavir at the regularly scheduled time.

Do not take a double dose to make up for a forgotten dose.

If you stop taking Aptivus
It has been shown that taking all doses at the appropriate times:
- greatly increases the effectiveness of your combination antiretroviral medicines
- reduces the chances of your HIV becoming resistant to your antiretroviral medicines

Therefore, it is important that you continue taking Aptivus correctly, as described above. Do NOT stop taking Aptivus unless your doctor instructs you to do so.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. It may be difficult to tell the difference between:
- side effects caused by Aptivus
- side effects caused by the other medicines you are also taking
- complications of HIV infection.

For this reason it is very important that you tell your doctor about any changes in your health.

Serious side effects associated with Aptivus:

- Abnormal liver function
    - Hepatitis and fatty liver
    - Liver failure. This can lead to death
    - Increased blood levels of bilirubin (a breakdown product of haemoglobin)

  You should inform your doctor if you experience:

    - Loss of appetite
    - Nausea (upset stomach)
    - Vomiting and/or jaundice

  which may be symptoms of abnormal liver function
- Bleeding
    - *Bleeding in the brain. This can lead to permanent disability or death, and has occurred in some patients treated with Aptivus in clinical trials. In the majority of these patients the bleeding may have had other causes. For example they had other medical conditions or were receiving other medicine that may have caused the bleeding.

Possible side effects:

Very common: may affect more than 1 in 10 people
- Diarrhoea
- Nausea (upset stomach)

Common: may affect up to 1 in 10 people
- Vomiting
- Abdominal pain (tummy pain)
- Flatulence (when you break wind more often)
- Tiredness
- Headache
- Mild rashes e.g. with hives or with flat or raised small red spots
- Increases in blood lipid (fat) levels
- Dyspepsia

Uncommon: may affect up to 1 in 100 people
- Reduction in red and white blood cells
- Reduction in blood platelets
- Allergic (hypersensitivity) reactions
- Decreased appetite
- Diabetes
- Increased blood sugar
- Increased blood levels of cholesterol
- Sleeplessness and other sleep disorders
- Sleepiness
- Dizziness
- Numbness and/or tingling and/or pain in the feet or hands
- Breathing difficulties
- Heartburn
- Inflammation of the pancreas
- Skin inflammation
- Itching
- Loss or gain of body fat and other changes in fat distribution (see below)
- Muscle cramp
- Muscle pain
- Kidney disease
- Flu like symptoms (feeling unwell)
- Fever
- Weight loss
- Increased blood levels of the pancreas enzyme amylase
- Increases in liver enzyme activity
- Hepatitis with liver cell damage due to influence of a toxin

Rare: may affect up to 1 in 1,000 people
- Liver failure (including fatal outcome)
- Hepatitis
- Fatty liver
- Increased blood levels of bilirubin (a breakdown product of haemoglobin)
- Dehydration (when your body does not have enough water)
- Thinning of the face
- Bleeding in the brain* (see above)
- Increased blood levels of the pancreas enzyme lipase

Further information on possible side effects related to combination antiretroviral treatment:
- Blood

  Combination antiretroviral therapy may also cause:
  - Raised lactic acid in the blood.
  - Raised sugar in the blood. The effect of insulin (used to treat diabetics to reduce blood sugar) may be reduced.
  - Hypertriglyceridaemia (increased triglycerides (fats) in the blood)
  - Hypercholesterolaemia (increased cholesterol in the blood)
- Bleeding
  - Increased bleeding. If you have haemophilia type A and B, you may experience increased bleeding. This may be in the skin or joints. If you suffer increased bleeding you should see your doctor immediately.

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck (‘buffalo hump’). The cause and long-term health effects of these conditions are not known at this time.

Muscle disorders
There have been reports of muscle pain, tenderness or weakness. These occur particularly when Aptivus or other protease inhibitors are taken together with nucleoside analogues. Rarely these muscle disorders have been serious, involving breakdown of muscle tissue (rhabdomyolysis).

Additional side effects in children and adolescents
The most common side effects were generally similar to those described in adults. Vomiting, rash and fever were observed more frequently in children than in adults.

Reporting of side effects
If you get any side effects, please talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Aptivus

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C). Once the bottle is opened the contents must be used within 60 days (stored below 25°C). You should write the date of opening the bottle on the label and/or outer carton.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Aptivus contains
- The active substance is tipranavir. Each capsule contains 250 mg tipranavir.
- The other ingredients are macrogolglycerol ricinoleate, ethanol (alcohol), mono/diglycerides of caprylic/capric acid, propylene glycol, purified water, trometamol and propyl gallate. The capsule shell contains gelatin, red iron oxide, propylene glycol, purified water, 'sorbitol special-glycerin blend' (d-sorbitol, 1,4 sorbitan, mannitol and glycerin) and titanium dioxide. The black printing ink contains propylene glycol, black iron oxide, polyvinyl acetate phthalate, macrogol and ammonium hydroxide.

What Aptivus looks like and contents of the pack
Aptivus soft capsules are pink coloured, oblong soft gelatin capsules with a black print imprint of 'TPV 250'. Each Aptivus capsule contains 250 mg of the active substance tipranavir. Aptivus is supplied in bottles containing 120 capsules.

Marketing Authorisation Holder

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Germany

Manufacturer

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This leaflet was last approved in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the user

Aptivus 100 mg/ml oral solution
tipranavir

Read all of this leaflet carefully before your child starts taking this medicine because it contains important information for your child.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your child's doctor or pharmacist.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as your child's.
- If your child gets any side effects, talk to your child's doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Aptivus is and what it is used for

Aptivus contains the active substance tipranavir. It belongs to a group of medicines called protease inhibitors and is used in the treatment of Human Immunodeficiency Virus (HIV) infection. . It blocks an enzyme called protease that is involved in the reproduction of HIV. When the enzyme is blocked, the virus does not reproduce normally, slowing down the infection. Your child must take Aptivus together with:

- low dose ritonavir (this helps Aptivus to reach a high enough level in your child's blood)
- other HIV medicines. Your child's doctor, together with you, will decide which other medicines your child should take. This will depend on, for example:
  - which other medicines your child has already taken for HIV
  - which medicines your child's HIV is resistant to. If your child's HIV is resistant to some HIV medicines, this means that the medicine will not work so well, or will not work at all.

Aptivus is specifically used for the treatment of HIV which is resistant to most other protease inhibitors. Before starting treatment, your child's doctor will have taken blood samples to test the resistance of your child's HIV. These tests will have confirmed that the HIV in your child's blood is resistant to most other protease inhibitors. Aptivus treatment is therefore appropriate for your child. Your child should not use Aptivus if they have never received antiretroviral therapy or have other antiretroviral options available.

Aptivus oral solution is indicated for:
- children from 2 to 12 years of age

2. What you need to know before your child takes Aptivus

Your child must take Aptivus in combination with low dose ritonavir and other antiretroviral medicines. It is therefore important that you know about these medicines too. You should therefore carefully read the Package Leaflets of ritonavir and your child's other antiretroviral

medicines. If you have any further questions about ritonavir or the other medicines your child is prescribed, please ask your child's doctor or pharmacist.

Do not give Aptivus
- if your child is allergic to tipranavir or any of the other ingredients of this medicine (listed in section 6)
- if your child has moderate to severe liver problems. Your child's doctor will take a blood sample to test how well your child's liver is working (your child's liver function). Depending on your child's liver function they may have to delay or stop Aptivus treatment
- if your child is currently taking products containing:
    - rifampicin (used to treat tuberculosis)
    - cisapride (used to treat stomach problems)
    - pimozide or sertindole (used to treat schizophrenia)
    - quetiapine (used to treat schizophrenia, bipolar disorder and major depressive disorder)
    - triazolam or oral midazolam (taken by mouth). These medicines are used to treat anxiety or sleep disorders
    - ergot derivatives (used to treat headaches)
    - astemizole or terfenadine (used to treat allergies or hay fever)
    - simvastatin or lovastatin (used to lower blood cholesterol)
    - amiodarone, bepridil, flecainide, propafenone or quinidine (used to treat heart disorders)
    - metoprolol (used to treat heart failure)
    - alfuzosin and sildenafil (when used to treat a rare blood vessel disorder characterized by increased pressure in the pulmonary artery)
    - colchicine (when used to treat gout flares in patients with kidney or liver disease).

Your child must not take products containing St John's wort (a herbal remedy for depression). This may stop Aptivus from working properly.

Warnings and precautions
Talk to your child's doctor or pharmacist before giving Aptivus to your child.

Tell your child's doctor if they have:
- type A or B haemophilia
- diabetes
- liver disease.

If your child has:
- high liver function tests results
- hepatitis B or C infection

your child is at increased risk of severe and potentially fatal liver damage while taking Aptivus. Your child's doctor will monitor their liver function by blood tests before and during Aptivus treatment. If your child has liver disease or hepatitis, their doctor will decide if they need additional testing. You should inform your child's doctor as soon as possible if you notice your child has the signs or symptoms of hepatitis:
- fever
- malaise (feeling generally unwell)
- nausea (upset stomach)
- vomiting
- abdominal pain
- tiredness
- jaundice (yellowing of the skin or the eyeballs)

<u>Aptivus is not a cure for HIV infection:</u>
You should know that your child may continue to develop infections and other illnesses associated with HIV disease. You should therefore remain in regular contact with your child's doctor. Your child

can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your child's doctor the precautions needed to avoid infecting other people.

Rash:
Mild to moderate rash, including:
- hives
- rash with flat or raised small red spots
- sensitivity to the sun

have been reported in approximately 1 in 10 patients receiving Aptivus. Some patients who developed rash also had:
- joint pain or stiffness
- throat tightness
- generalized itching

Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your child's doctor if you notice changes in body fat.

Your child's doctor may decide to monitor their levels of blood lipids (fats) before and during Aptivus treatment.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection (for example fever, enlarged lymph nodes), please inform your child's doctor immediately.

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after your child starts taking medicines for the treatment of your child's HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your child's doctor immediately to seek necessary treatment.

Tell your child's doctor if your child experiences fainting or a sensation of abnormal heart beats. Aptivus in combination with low dose ritonavir may cause changes in your child's heart rhythm and the electrical activity of your child's heart. These changes may be seen on an ECG (electrocardiogram).

Bone problems: Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your child's doctor.

Children and adolescents
Aptivus should neither be used by children under 2 years of age nor by adolescents 12 years of age or older.

Aptivus oral solution contains vitamin E. Your child should not take any additional vitamin E supplements.

Other medicines and Aptivus
Tell your child's doctor or pharmacist if your child is taking, has recently taken or might take any other medicines, including medicines obtained without a prescription.

This is **very important**. If your child takes other medicines at the same time as Aptivus and ritonavir, this can strengthen or weaken the effect of the medicines. These effects are called interactions, and can lead to serious side effects, or prevent proper control of other conditions your child may have.

Interactions with other HIV medicines:
- etravirine belongs to a class of HIV medicines called non-nucleoside reverse transcriptase inhibitors (NNRTIs). Taking Aptivus with etravirine is not recommended.

- abacavir and zidovudine. These belong to a class of HIV medicines called nucleoside reverse transcriptase inhibitors (NRTIs). Your child's doctor will only prescribe them abacavir and zidovudine if they are unable to take other NRTIs.

- didanosine: If your child is taking didanosine enteric coated tablets, they should take them at least two hours before or after Aptivus.

- emtricitabine: If your child is taking emtricitabine your child's kidney function should be checked before initiation of Aptivus.

- rilpivirine: If your child is taking rilpivirine, your child's doctor will monitor your child closely.

- Protease Inhibitors (PIs): Taking Aptivus may cause large decreases in the blood levels of other HIV protease inhibitors. For example the protease inhibitors amprenavir, atazanavir, lopinavir and saquinavir will be decreased.
  Taking Aptivus, with atazanavir, may cause the blood levels of Aptivus and ritonavir to increase a lot.
  Your child's doctor will carefully consider whether to treat them with combinations of Aptivus and protease inhibitors.

Other medicines with which Aptivus may interact include:
- oral contraceptives/hormone replacement therapy (HRT): If your child is taking the contraceptive pill to prevent pregnancy they should use an additional or different type of contraception (e.g. barrier contraception like condoms). Generally, it is not recommended to take Aptivus, with ritonavir, together with oral contraceptives or hormone replacement therapy (HRT). You should check with your child's doctor if they do wish to continue taking oral contraceptives or HRT. If your child uses oral contraceptives or HRT they have an increased chance of developing a skin rash while taking Aptivus. If a rash occurs, it is usually mild to moderate. You should talk to your child's doctor as they may need to temporarily stop taking either Aptivus or their oral contraceptives or HRT
- carbamazepine, phenobarbital and phenytoin (used to treat epilepsy). These may decrease the effectiveness of Aptivus.
- sildenafil, vardenafil, tadalafil (medicines used to produce and maintain an erection). The effects of sildenafil and vardenafil are likely to be increased if taken with Aptivus. Tadalafil should not be prescribed until Aptivus has been taken for 7 days or more.
- omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole (proton pump inhibitors used to reduce the gastric acid production)
- metronidazole (used to treat infections)
- disulfiram (used to treat alcohol dependence)
- buprenorphine/naloxone (medicines used to treat severe pain)
- cyclosporin, tacrolimus, sirolimus (used to prevent organ rejection (to suppress the immune system))
- warfarin (used to treat and prevent thrombosis)

- digoxin (used to treat heart arrhythmias and heart failure)
- antifungal medications including fluconazole, itraconazole, ketoconazole or voriconazole

The following medicines are not recommended:
- fluticasone (used to treat asthma)
- atorvastatin (used to lower blood cholesterol)
- salmeterol (used to achieve long-term asthma control, bronchospasm prevention with COPD)
- bosentan (used to treat pulmonary artery hypertension)
- halofantrine or lumefantrine (used to treat malaria)
- tolterodine (used to treat overactive bladder (with symptoms of urinary frequency, urgency, or urge incontinence))
- boceprevir and telaprevir (used to treat hepatitis C)
- cobicistat and products containing cobicistat (used to increase effectiveness of HIV medicines).

Aptivus may lead to a loss of effectiveness of some medicines including:
- methadone, meperidine (pethidine), used as morphine substitutes

Your child's doctor may have to increase or decrease the dose of other medicines which they take together with Aptivus. Examples include:
- rifabutin and clarithromycin (antibiotics)
- theophylline (used to treat asthma)
- desipramine, trazodone and bupropion (used to treat depression; bupropion is also used for smoking cessation)
- midazolam (when given by injection); midazolam is a sedative used to treat anxiety and to help your child sleep
- rosuvastatin or pravastatin (used to lower blood cholesterol)
- colchicine (used to treat gout flares with normal kidney and liver function).

If your child takes aluminium- and magnesium-based antacid (used to treat dyspepsia/ gastrooesophageal reflux), the time interval between Aptivus and antacid should be at least two hours.

Tell your child's doctor if your child receives medicines such as blood-thinning agents, or if your child is taking vitamin E. Your child's doctor may wish to consider certain precautionary measures in such circumstances.

Pregnancy, breast-feeding and fertility
If your child is pregnant or breast-feeding, you think your child may be pregnant or is planning to have a baby, ask your child's doctor or pharmacist for advice before giving this medicine. It is not known whether Aptivus may be used safely during pregnancy. Your child must not breast-feed the baby because it is possible that the baby can become HIV-infected through the breast milk. See also Section 2, under "Oral contraceptives/hormone replacement therapy (HRT)".

Driving and using machines
Some of the side effects of Aptivus may affect your child's ability to drive or operate machinery (e.g. dizziness and sleepiness). If affected, your child should not drive or operate machinery.

3. How to take Aptivus

Always give your child this medicine exactly as the doctor has advised. Check with your child's doctor or pharmacist if you are not sure. Your child must take Aptivus together with ritonavir.

Aptivus oral solution should be taken with food.

The dose for children, aged 2 to 12 years, will be calculated by the doctor. This will be based on the child's body surface area in metres squared. The dose for children should not exceed 5 ml (500 mg) twice a day. Be sure your child's doctor clearly informs you what the correct dose for your child

should be. You should measure the exact dose using the supplied measuring syringe and adapter, as follows:

1. Check that the oral solution is clear (see below).
2. Open the bottle by pressing down on the cap and turning it in an anti-clockwise direction.
3. Remove the syringe cap covering the tip of the oral syringe (the cap will not be attached if this is the first time you are using the syringe).
4. Insert the oral syringe into the adapter located in the neck of the bottle. Make sure the oral syringe is tightly inserted. The maximum volume you can withdraw at one time is 5 ml (equivalent to 500 mg tipranavir), which is the maximum single dose for a child with BSA (Calculated body surface area) > 1.33 m^2
5. Turn the bottle upside down and gently withdraw the required amount of Aptivus oral solution.
6. Gently empty Aptivus oral solution from the syringe into your child's mouth.
7. After use of the oral syringe, replace the syringe cap.

Before giving Aptivus you should check that the oral solution is clear. Crystals may be seen as a paper-thin layer at the bottom of the bottle when it is stored upright. There may be other particles at the bottom of the bottle. A small amount of crystals does not affect the strength or safety of your child's medicine.

You should return the bottle to your child's pharmacist or doctor for a replacement as soon as possible if:
- there is more than a thin layer of crystals at the bottom of the bottle, or
- you are uncertain about the amount of crystals you see or
- any other particles are visible.

Until you exchange the bottle, please continue to give your child their usual doses of Aptivus oral solution.

Your child will always have to take Aptivus in combination with other antiretroviral medicines. You should follow the instructions for these medicines within the supplied Package Leaflets.

Your child should continue to take Aptivus for as long as your child's doctor tells him/her. At the age of 12 years, children treated with Aptivus should be switched from the oral solution to the capsules.

If your child takes more Aptivus than he/she should
Inform your child's doctor as soon as possible if they take more than the prescribed dose of Aptivus.

If your child forgets to take Aptivus
If your child misses a dose of Aptivus or ritonavir by more than 5 hours, wait and then give the next dose of Aptivus and ritonavir at the regularly scheduled time. If your child misses a dose of Aptivus and/or ritonavir by less than 5 hours, give the missed dose immediately. Then give the next dose of Aptivus and ritonavir at the regularly scheduled time.

Do not give a double dose to make up for a forgotten dose.

If your child stops taking Aptivus
It has been shown that taking all doses at the appropriate times:
- greatly increases the effectiveness of your child's combination antiretroviral medicines
- reduces the chances of your child's HIV becoming resistant to his/her antiretroviral medicines.

Therefore, it is important that your child continues taking Aptivus correctly, as described above. Your child must NOT stop taking Aptivus unless your child's doctor instructs to do so.

If you have any further questions on the use of this medicine, ask your child's doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. It may be difficult to tell the difference between:
- side effects caused by Aptivus
- side effects caused by the other medicines your child is also taking
- complications of HIV infection.

For this reason it is very important that you tell your child's doctor about any changes in their health.

Serious side effects associated with Aptivus:

- Abnormal liver function
    - Hepatitis and fatty liver
    - Liver failure. This can lead to death
    - Increased blood levels of bilirubin (a breakdown product of haemoglobin)

  You should inform your child's doctor if they experience:
    - Loss of appetite
    - Nausea (upset stomach)
    - Vomiting and/or jaundice

  which may be symptoms of abnormal liver function
- Bleeding
    - * Bleeding in the brain. This can lead to permanent disability or death, and has occurred in some patients treated with Aptivus in clinical trials. In the majority of these patients the bleeding may have had other causes. For example they had other medical conditions or were receiving other medicine that may have caused the bleeding.

Possible side effects:

<u>Very common: may affect more than 1 in 10 people</u>
- Diarrhoea
- Nausea (upset stomach)

<u>Common: may affect up to 1 in 10 people</u>
- Vomiting
- Abdominal pain (tummy pain)
- Flatulence (breaking wind more often)
- Tiredness
- Headache
- Mild rashes e.g. with hives or with flat or raised small red spots
- Increases in blood lipid (fat) levels
- Dyspepsia

<u>Uncommon: may affect up to 1 in 100 people</u>
- Reduction in red and white blood cells
- Reduction in blood platelets
- Allergic (hypersensitivity) reactions
- Decreased appetite
- Diabetes
- Increased blood sugar
- Increased blood levels of cholesterol
- Sleeplessness and other sleep disorders
- Sleepiness
- Dizziness
- Numbness and/or tingling and/or pain in the feet or hands
- Breathing difficulties

- Heartburn
- Inflammation of the pancreas
- Skin inflammation
- Itching
- Loss or gain of body fat and other changes in fat distribution (see below)
- Muscle cramp
- Muscle pain
- Kidney disease
- Flu like symptoms (feeling unwell)
- Fever
- Weight loss
- Increased blood levels of the pancreas enzyme amylase
- Increases in liver enzyme activity
- Hepatitis with liver cell damage due to influence of a toxin

Rare: may affect up to 1 in 1,000 people
- Liver failure (including fatal outcome)
- Hepatitis
- Fatty liver
- Increased blood levels of bilirubin (a breakdown product of haemoglobin)
- Dehydration (when the body does not have enough water)
- Thinning of the face
- Bleeding in the brain* (see above)
- Increased blood levels of the pancreas enzyme lipase

Further information on possible side effects related to combination antiretroviral treatment:
- Blood
  Combination antiretroviral therapy may also cause:
  - Raised lactic acid in the blood.
  - Raised sugar in the blood. The effect of insulin (used to treat diabetics to reduce blood sugar) may be reduced.
  - Hypertriglyceridaemia (increased triglycerides (fats) in the blood)
  - Hypercholesterolaemia (increased cholesterol in the blood)
- Bleeding
  - Increased bleeding. If your child has haemophilia type A and B, they may experience increased bleeding. This may be in the skin or joints. If your child suffers increased bleeding you should see your child's doctor immediately.

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck ('buffalo hump'). The cause and long-term health effects of these conditions are not known at this time.

Muscle disorders
There have been reports of muscle pain, tenderness or weakness. These occur particularly when Aptivus or other protease inhibitors are taken together with nucleoside analogues. Rarely these muscle disorders have been serious, involving breakdown of muscle tissue (rhabdomyolysis).

Additional side effects in children and adolescents
The most common side effects were generally similar to those described in adults. Vomiting, rash and fever were observed more frequently in children than in adults.

Reporting of side effects
If your child gets any side effects, please talk to your child's doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Aptivus

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle after EXP. The expiry date refers to the last day of that month.

Do not store below 15°C. Do not refrigerate or freeze. Once the bottle is opened your child should use the medicine within 60 days. You should write the date of opening the bottle on the label and/or outer carton. Keep the container in the outer carton.
If you notice more than a thin layer of crystals at the bottom of the bottle you should:
- give the next dose
- return the bottle to the pharmacist or doctor as soon as possible for a fresh supply.

Do not throw away any medicines via wastewater or household waste. Ask your child's pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Aptivus contains
- The active substance is tipranavir. Each ml contains 100 mg tipranavir.
- The other ingredients are macrogol, vitamin E polyethylene glycol succinate, purified water, propylene glycol, mono/diglycerides of caprylic/capric acid, sucralose, ascorbic acid, Butter Mint and Butter Toffee flavourings.

What Aptivus looks like and contents of the pack
Aptivus oral solution is a clear yellow liquid.

Aptivus oral solution is supplied in amber glass bottles containing 95 ml of oral solution. A 5 ml oral syringe and adapter is supplied for dosing.

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Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: http://www.ema.europa.eu.