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Boehringer Ingelheim Limited · Ellesfield Avenue, Bracknell, Berkshire RG12 8YS

Boehringer Ingelheim Limited
Medical Division

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Important Safety Information: Intracranial Haemorrhage (ICH) in Patients Receiving APTIVUS (tipranavir)

Dr. C.S. de Wet
Telephone +44 (0) 1344 742697
Telefax +44 (0) 1344 741298

Ellesfield Avenue
Bracknell, Berkshire RG12 8YS
Telephone +44 (0) 1344 424600
Telefax +44 (0) 1344 741444
www.boehringer-ingelheim.co.uk

Dear Health Care Professional,

Boehringer Ingelheim together with the Irish Medicines Board is writing to inform you of important new safety information for APTIVUS (tipranavir), 250 mg Soft Capsules, a non-peptidic protease inhibitor. APTIVUS co-administered with low dose ritonavir is indicated for combination antiretroviral treatment of HIV-1 infection in highly pre-treated adult patients with virus resistant to multiple protease inhibitors.

- Boehringer Ingelheim (BI) has received 14 reports of intracranial haemorrhage (ICH), including 8 fatalities, in 6840 HIV-1 infected patients receiving APTIVUS in clinical trials.

- Many of the patients experiencing ICH in the APTIVUS clinical development program had other medical conditions (CNS lesions, head trauma, recent neurosurgery, coagulopathy, hypertension or alcohol abuse) or were receiving concomitant medications, including anti-coagulants and anti-platelet agents, that may have caused or contributed to these events. However in some cases the role of APTIVUS cannot be excluded.

- No pattern of abnormal haematologic 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.

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- An increased risk of ICH has previously been observed in patients with advanced HIV-1 disease / AIDS such as those treated in the APTIVUS clinical trials.

- 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 medications known to increase the risk of bleeding such as antiplatelet agents or anticoagulants.

— Further investigations are ongoing.

The following information on ICH risk has been added to section 4.4 (Special Warnings and special precautions for use) and section 4.8 (Undesirable effects) of the APTIVUS Summary of Product Characteristics (SPC). These changes to the SPC have been agreed upon with the Committee for Medicinal Products for Human Use (CHMP), the scientific committee of the European Medicines Agency (EMEA), and are currently awaiting formal approval by the European Commission. A copy of the revised APTIVUS SPC is attached to this letter.

Section 4.4 (Special Warnings and special precautions for use) and section 4.8 (Undesirable effects)

Bleeding

Fatal and non-fatal intracranial haemorrhage (ICH) have been reported in patients receiving APTIVUS, many of whom had other medical conditions or were receiving concomitant medications 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.

APTIVUS, co-administered with low dose ritonavir, should be used with caution in patients who may be at risk of increased bleeding

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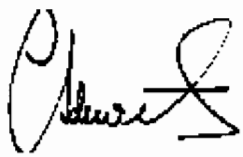
from trauma, surgery or other medical conditions, or who are receiving medications known to increase the risk of bleeding such as antiplatelet agents or anticoagulants.

In addition, the pre-existing wording on bleeding risk in general, contained within section 4.8 of the original SPC, has also been added to section 4.4, directly preceding the above wording on ICH risk. Please refer to the attached SPC.

Boehringer-Ingelheim, in collaboration with the EMEA, has also similarly revised the APTIVUS Package Leaflet (PL) that provides patients with the most important information they need to know about APTIVUS. A copy of this revised PL is also attached to this letter for your reference.

Any suspected adverse reactions should be notified to the company and/or Irish Medicines Board in the usual way.

Yours faithfully



C.S. de Wet M.B., Ch.B., MPharm. Med., F.F.P.M. MIoD
Medical Director UK & Ireland

Aptivus® 250 mg soft capsules

Republic of Ireland

Tipranavir

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.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule.

Each capsule is pink and is imprinted with TPV 250.

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 adult patients with virus resistant to multiple protease inhibitors.

This indication is based on the results of two phase III studies, performed in highly pre-treated patients (median number of 12 prior antiretroviral agents) with virus resistant to protease inhibitors (see details of resistance profile of patients' HIV at baseline in section 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.

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.

Adults:
The recommended dose of APTIVUS is 500 mg, co-administered with 200 mg ritonavir (low dose ritonavir), twice daily.

Paediatrics:
Safety and efficacy of APTIVUS in this population has not yet been established.

General:
APTIVUS soft capsules co-administered with low dose ritonavir should be taken with food (see section 5.2).

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 should not be used in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) (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).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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

Rifampicin should not be used with APTIVUS because co-administration may cause large decreases in tipranavir concentrations which may in turn significantly decrease the tipranavir therapeutic effect (see section 4.5).

Herbal preparations containing St John's wort (*Hypericum perforatum*) must not be used while taking APTIVUS 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 is contraindicated. These active substances include antiarrhythmics (amiodarone, bepridil, quinidine), antihistamines (astemizole, terfenadine), ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine), gastrointestinal motility agents (cisapride), neuroleptics (pimozide, sertindole), sedatives/hypnotics (triazolam) and HMG-CoA reductase inhibitors (simvastatin and lovastatin). In addition, co-administration of APTIVUS with low dose ritonavir, with drugs that are highly dependent on CYP2D6 for clearance, such as the antiarrhythmics flecainide and propafenone, is contraindicated (see section 4.5).

4.4 Special warnings and special 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.

Doses of ritonavir lower than 200 mg twice daily should not be used as they might alter the efficacy profile of the combination.

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.

Patients should be advised that current antiretroviral therapy has not been proven to prevent the risk of transmission of HIV to others through blood or sexual contact. Appropriate precautions should continue to be employed.

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. In general, caution should be exercised in the administration and monitoring of APTIVUS in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other therapy.

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 events. 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 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. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Patients with mild hepatic impairment (Child-Pugh Class A) should be closely monitored.

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 medications. Patients with signs or symptoms of hepatitis should discontinue APTIVUS/ritonavir treatment and seek medical evaluation. Caution should be exercised when administering APTIVUS, to patients with liver enzyme abnormalities or 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 permanently discontinued in patients experiencing ASAT or ALAT elevations greater than 10X ULN, or developing signs or symptoms of clinical hepatitis during therapy.

Liver Monitoring:
Monitoring of hepatic tests should be done prior to initiation of therapy, after two, four and eight weeks, and then every eight to twelve weeks thereafter. Increased monitoring (i.e. every two weeks during the first three months of treatment and monthly 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.

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. Haemaophiliac patients should therefore be made aware of the possibility of increased bleeding.

Bleeding: RESIST participants receiving APTIVUS/ritonavir tended to have an increased risk of bleeding; at 24 weeks the relative risk was 1.98 (95% CI=1.03, 3.80). 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 studied.

Fatal and non-fatal intracranial haemorrhage (ICH) have been reported in patients receiving APTIVUS, many of whom had other medical conditions or were receiving concomitant medications 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.

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 medications known to increase the risk of bleeding such as antiplatelet agents or anticoagulants.

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 drug related factors 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.

APTIVUS soft capsules contain macrogolglycerol ricinoleate which may cause stomach upset and diarrhoea.

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. In Phase II and III trials rash was observed in 14% of females and in 8-10% of males 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.

Interactions: The interaction profile of APTIVUS, co-administered with low dose ritonavir, is complex. For a description of the mechanisms and potential mechanisms contributing to the interaction profile of APTIVUS, 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 (see section 4.5). No data are currently available on interactions of APTIVUS, co-administered with low dose ritonavir, with protease inhibitors other than those listed above. Therefore, the co-administration of APTIVUS, co-administered with low dose ritonavir, with protease inhibitors is not recommended.

Midazolam: When used intravenously midazolam should be administered with caution due to the risk of increased midazolam levels and prolonged half-life in patients taking APTIVUS co-administered with low dose ritonavir.

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.

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 (eg metronidazole).

Fluticasone: Concomitant use of APTIVUS, 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: APTIVUS, 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. However, if atorvastatin is specifically required for patient management, careful monitoring is necessary.

Due to APTIVUS containing small amounts of sorbitol, patients with rare hereditary problems of fructose intolerance should not take this medicine.

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.

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 adverse 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 events are detailed in this section, and listed in section 4.3.

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/ritonavir on CYP 2D6 is inhibition, because ritonavir is a CYP 2D6 inhibitor. The *in vivo* net effect of tipranavir/ritonavir on CYP 1A2, CYP 2C9 and CYP 2C19 is not known. Data are not available to indicate whether tipranavir inhibits or induces glucuronosyl transferases and whether tipranavir induces CYP 1A2, CYP 2C9 and CYP 2C19.

Tipranavir is a Pgp substrate, a weak Pgp inhibitor and appears to be a potent Pgp inducer as well. Data suggest that, although ritonavir is a Pgp inhibitor, the net effect of APTIVUS, co-administered with low dose ritonavir, at the proposed dose regimen at steady-state, is Pgp induction.

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 Pgp. The net effect will vary depending on the relative affinity of the co-administered drugs for CYP3A and Pgp, and the extent of intestinal first-pass metabolism/efflux.

Tipranavir is metabolised by CYP3A and is a Pgp substrate. Co-administration of APTIVUS and agents that induce CYP3A and/or Pgp 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 Pgp may increase tipranavir plasma concentrations.

Data are not yet available to indicate whether tipranavir inhibits or induces glucuronosyl transferases.

Nucleoside reverse transcriptase inhibitors: 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 and Zidovudine: APTIVUS, co-administered with low dose ritonavir, decreases the AUC of abacavir by approximately 40% and the AUC of zidovudine by approximately 35%. There is no impact on glucuronidated-ZDV levels. The clinical relevance of these reductions has not been established, but may decrease the efficacy of these antiretroviral agents. Therefore the concomitant use of tipranavir, co-administered with low dose ritonavir, with either abacavir or zidovudine is not recommended unless there are no other available NRTIs suitable for patient management. In such cases no dosage adjustment of abacavir or zidovudine can be recommended.

Didanosine: APTIVUS, co-administered with low dose ritonavir, causes a reduction in the AUC of didanosine. The clinical relevance of the reduction in didanosine levels has not been established. 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.

Lamivudine and stavudine: APTIVUS, co-administered with low dose ritonavir, does not cause a significant change in the AUC of lamivudine or stavudine. No dosage adjustment of lamivudine or stavudine is recommended.

Nucleotide reverse transcriptase inhibitors:
Tenofovir: APTIVUS, co-administered with low dose ritonavir, did not cause a significant change in the plasma concentrations of tenofovir. No dosage adjustment of tenofovir is recommended.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs):
Nevirapine, efavirenz: The data currently available appear to suggest no significant interaction between nevirapine or efavirenz and APTIVUS co-administered with low dose ritonavir. However, these current data are limited and do not allow to draw definitive conclusion on the interactions between NNRTIs and APTIVUS (co-administered with low dose ritonavir). Therefore, while further information on interactions are currently generated and awaited, caution should be used when combining efavirenz or nevirapine with APTIVUS (co-administered with low dose ritonavir).

Protease Inhibitors:
Amprenavir, lopinavir, saquinavir: In a clinical study of dual-boosted protease inhibitor combination therapy in multiple-treatment experienced HIV-positive adults, APTIVUS, co-administered with low dose ritonavir, caused a 55%, 70% and 78% reduction in the C_{min} of amprenavir, lopinavir and saquinavir, respectively. Therefore the concomitant administration of APTIVUS, co-administered with low dose ritonavir, with amprenavir/ritonavir, lopinavir/ritonavir or saquinavir/ritonavir, is not recommended, as the clinical relevance of the reduction in their levels has not been established. If the combination is nevertheless considered necessary, a monitoring of the plasma levels of these protease inhibitors is strongly encouraged.

No data are currently available on interactions of APTIVUS, co-administered with low dose ritonavir, with protease inhibitors other than those listed above. Hence their

combination with tipranavir co-administered with low dose ritonavir, is not recommended (see section 4.4).

Antifungals:
Fluconazole: APTIVUS, co-administered with low dose ritonavir, does not substantially affect the steady-state pharmacokinetics of fluconazole. Fluconazole increases the AUC and C_{min} of tipranavir by 56% and 104%, respectively, when compared to historical data. No dosage adjustments are recommended. Fluconazole doses >200 mg/day are not recommended.

Itraconazole/ketoconazole: Based on theoretical considerations APTIVUS, co-administered with low dose ritonavir, is expected to increase itraconazole or ketoconazole concentrations. Itraconazole or ketoconazole should be used with caution (doses >200 mg/day are not recommended).

Voriconazole: Due to multiple enzyme systems being involved in voriconazole metabolism, it is difficult to predict the interaction.

HMG CoA reductase inhibitors:
Simvastatin and lovastatin: The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A for metabolism, thus 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).

Atorvastatin: APTIVUS, co-administered with low dose ritonavir, increases the plasma concentrations of single dose atorvastatin by approximately 8-10 fold and reduces the AUCs of its metabolites by approximately 85 %. Atorvastatin does not significantly change the AUC, C_{max} or C_{min} of tipranavir. The combination is not recommended. Other HMG-CoA reductase inhibitors should be considered such as pravastatin, fluvastatin or rosuvastatin. However, if atorvastatin is specifically required for patient management, careful monitoring is necessary (see section 4.4).

CYP isoenzyme inducers:
Rifampicin: Co-administration of protease inhibitors with rifampicin substantially decreases protease inhibitor concentrations. In the case of APTIVUS 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. Concomitant use of APTIVUS and rifampicin is therefore contraindicated (see section 4.3). Alternate antimycobacterial agents such as rifabutin should be considered.

Rifabutin: APTIVUS, co-administered with low dose ritonavir, increases plasma concentrations of rifabutin by up to 3 fold, and its active metabolite by up to 20 fold. Rifabutin increases the C_{min} of tipranavir by 16 %. 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/ritonavir should be closely monitored for emergence of adverse events associated with rifabutin therapy. Further dosage reduction may be necessary.

St John's wort (Hypericum perforatum): Plasma levels 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 should not be used concomitantly with APTIVUS. If a patient is already taking St John's wort, stop St John's wort, check viral levels and if possible tipranavir levels. Tipranavir levels may increase on stopping St John's wort, and the dose of APTIVUS may need adjusting. The inducing effect of St John's wort may persist for at least 2 weeks after cessation of treatment (see section 4.3).

CYP isoenzyme inhibitors:
Clarithromycin: APTIVUS, co-administered with low dose ritonavir, increases the AUC and C_{min} of clarithromycin by 19% and 68%, respectively, and decreases the AUC of the 14-hydroxy active metabolite by over 95%. 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. Clarithromycin increases the C_{min} of tipranavir by more than 100%. This large increase in 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. For patients with renal impairment the following dosage adjustments should be considered: For patients with CL_{CR} 30 to 60 ml/min the dose of clarithromycin should be reduced by 50 %. For patients with CL_{CR} < 30 ml/min the dose of clarithromycin should be decreased by 75 %. No dosage adjustments for patients with normal renal function are necessary.

Other agents:

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 is contraindicated. These active substances include antiarrhythmics (amiodarone, bepridil, quinidine), antihistamines (astemizole, terfenadine), ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine), gastointestinal motility agents (cisapride), neuroleptics (pimozide, sertindole) and sedatives/hypnotics (triazolam) (see section 4.3).

In addition, co-administration of APTIVUS with low dose ritonavir, with drugs that are highly dependent on CYP2D6 for clearance, such as the antiarrhythmics flecainide and propafenone, is contraindicated (see section 4.3).

Some anti-infectives are not recommended (halofantrine, lumefantrine) as well as miscellaneous agents (tolterodine) (see section 4.4).

Oral contraceptives/oestrogens:
APTIVUS, co-administered with low dose ritonavir, decreases the AUC and C_{max} of ethinyl-oestradiol by 50 %, but does not significantly alter the pharmacokinetic behaviour of norethindrone. 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 section 4.4 and section 4.6).

Phosphodiesterase 5 (PDE5) inhibitors (sildenafil, tadalafil, vardenafil)
Particular caution should be used when prescribing phosphodiesterase (PDE5) inhibitors (eg sildenafil, vardenafil or tadalafil) in patients receiving APTIVUS co-administered with

low dose ritonavir. Co-administration of APTIVUS 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.

Narcotic analgesics (Methadone/Meperidine): Co-administration of APTIVUS and low dose ritonavir with methadone is expected to decrease methadone concentrations. Therefore in such cases, patients should be monitored for opiate abstinence syndrome. Dosage of methadone may need to be increased. APTIVUS, 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 (eg seizures).

Immunosuppressants (cyclosporin, tacrolimus, sirolimus): Concentrations of cyclosporin, tacrolimus, or sirolimus cannot be predicted when co-administered with APTIVUS co-administered with low dose ritonavir, due to conflicting effect of APTIVUS, co-administered with low dose ritonavir, on CYP 3A and Pgp. More frequent concentration monitoring of these medicinal products is recommended until blood levels have been stabilised.

Warfarin and other oral anticoagulants: The effect of co-administration of APTIVUS with low dose ritonavir on S-warfarin cannot be predicted due to conflicting effects of tipranavir and ritonavir on CYP 2C9. APTIVUS co-administered with low dose ritonavir, may increase INR (International Normalised Ratio) values, and may increase risk of bleeding. A close clinical and biological (INR measurement) monitoring is recommended when these medicinal products are combined.

Antacids: When APTIVUS, co-administered with low dose ritonavir, was co-administered with 20 ml of aluminium- and magnesium-based liquid antacid, tipranavir AUC_{12h}, C_{max} and C_{min} were reduced by 25-29 %. Dosing of APTIVUS, co-administered with low dose ritonavir, with antacids should be separated by at least a two hours time interval.

To date, no data are available with proton pump inhibitors or H2-receptor antagonists. However, reduced plasma concentrations of tipranavir may result due to increased gastric pH if these medicinal products are administered with APTIVUS co-administered with low dose ritonavir. Caution should be exercised.

Theophylline: APTIVUS, co-administered with low dose ritonavir, is expected to decrease theophylline concentrations. Increased dosage of theophylline may be required and therapeutic monitoring should be considered.

Desipramine: APTIVUS, co-administered with low dose ritonavir, is expected to increase desipramine concentrations. Dosage reduction and concentration monitoring of desipramine is recommended.

Loperamide: 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 pharmacokinetic analysis showed that the AUC and C_{max} of loperamide are reduced by

51% and 61%, respectively, and the C_{min} of tipranavir by 26%. The clinical relevance of these changes is unknown.

Fluticasone propionate (interaction 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 eg budesonide. Consequently, concomitant administration of tipranavir, 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 Pregnancy and lactation

There are no adequate data from the use of APTIVUS 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.

APTIVUS adversely interacts with oral contraceptives. Therefore, an alternative, effective, safe method of contraception should be used during treatment.

Consistent with the recommendation that HIV-infected mothers 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.

APTIVUS soft capsules contain small amounts of alcohol (7% ethanol, ie 100 mg per capsule or 200 mg per dose).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Patients should be informed that APTIVUS soft capsules contain small amounts of alcohol (7% ethanol, ie 100 mg per capsule or 200 mg per dose).

4.8 Undesirable effects

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 APTIVUS/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.

Tipranavir, co-administered with low dose ritonavir has been studied in a total of 1854 HIV-positive adults as combination therapy in clinical studies. Of these 1397 patients received the dose of 500 mg/200 mg twice daily. 761 adults, including 385 in the RESIST-1 and RESIST-2 Phase III pivotal trials, have been treated for at least 24 weeks.

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

Hepatotoxicity: After 24 weeks of follow-up, the frequency of Grade 3 or 4 ALAT and/or ASAT abnormalities was higher in APTIVUS/ritonavir patients compared with comparator arm patients (6.2 % and 2.5 %, 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 APTIVUS/ritonavir.

Hyperlipidaemia: Grade 3 or 4 elevations of triglycerides occurred more frequently in the APTIVUS/ritonavir arm compared with the comparator arm. At 24 weeks these rates were 20.8 % of patients in the APTIVUS/ritonavir arm and 11.2 % in the comparator arm.

Bleeding: RESIST participants receiving APTIVUS/ritonavir tended to have an increased risk of bleeding; at 24 weeks the relative risk was 1.98 (95% CI=1.03, 3.80). 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 studied.

Fatal and non-fatal intracranial haemorrhage (ICH) have been reported in patients receiving APTIVUS, many of whom had other medical conditions or were receiving concomitant medications 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.

Rash: An interaction study in women between APTIVUS, 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 APTIVUS/ritonavir and comparator arms (see section 4.4). No cases of Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis have been reported in the clinical development programme of APTIVUS.

The most frequent adverse reactions of any intensity (Grades 1-4) reported in the Phase III clinical studies in the APTIVUS/ritonavir arms (n=746) are listed below by system organ class and frequency according to the following categories:

Very common > 1/10, common > 1/100 – <1/10

Metabolism and nutrition disorders:
Common: hypertriglyceridaemia, hyperlipidaemia, anorexia.

Nervous system disorders:
Common: headache.

Gastro-intestinal disorders:
Very common: diarrhoea, nausea.
Common: vomiting, flatulence, abdominal distension, abdominal pain, loose stools, dyspepsia.

Skin and subcutaneous tissue disorders
Common: rash, pruritus.

General disorders
Common: fatigue.

Clinically meaningful adverse reactions of moderate to severe intensity occurring in less than 1% (<1/100) of adult patients in all Phase II and III trials treated with the 500 mg/200 mg tipranavir/ritonavir dose (n=1397) are listed below by system organ class and frequency according to the following categories:

Uncommon > 1/1000 – <1/100, rare <1/1000

Blood and lymphatic system disorders:
Uncommon: anaemia, neutropenia, thrombocytopenia.

Immune system disorders:
Uncommon: hypersensitivity.

Metabolism and nutrition disorders:
Uncommon: decreased appetite, diabetes mellitus, hyperamylasaemia, hypercholesterolaemia.
Rare: dehydration, facial wasting, hyperglycaemia.

Psychiatric disorders:
Uncommon: insomnia, sleep disorder.

Nervous system disorders:
Uncommon: dizziness, neuropathy peripheral, somnolence.

Respiratory, thoracic and mediastinal disorders:
Uncommon: dyspnoea.

Gastrointestinal disorders:
Uncommon: gastrooesophageal reflux disease, pancreatitis.

Hepatobiliary disorders:
Uncommon: hepatitis.
Rare: hepatic failure (including fatal outcome).

Skin and subcutaneous system disorders:
Uncommon: exanthem, lipoatrophy, lipodystrophy acquired, lipohypertrophy.

Musculoskeletal and connective tissue disorders:
Uncommon: muscle cramp, myalgia.

Renal and urinary disorders:
Uncommon: renal insufficiency.

General disorders:
Uncommon: influenza like illness, malaise, pyrexia.

Investigations:
Uncommon: hepatic enzymes increased (ALAT, ASAT), liver function test abnormal (ALAT, ASAT), weight decreased.
Rare: lipase increased.

Laboratory abnormalities

Frequencies of marked clinical laboratory abnormalities (Grade 3 or 4) reported in at least 2 % of patients in the APTIVUS/ritonavir arms in the phase III clinical studies (RESIST-1 and RESIST-2) were increased ASAT (4.0 %), increased ALAT (5.9 %), increased amylase (4.5 %), increased cholesterol (3.3 %), increased triglycerides (20.8 %), and decreased white blood cell count (3.6 %).

In clinical trials extending up to 48-weeks, ALT and/or AST elevations continued to increase to 9.8% with APTIVUS/ritonavir as compared to 3.0% with comparator PI/ritonavir.

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 (see section 4.4).

4.9 Overdose

There is no known antidote for APTIVUS 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 drug. 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: protease inhibitor, ATC code: J05A E09

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 is also effective at inhibiting the replication of M-tropic strains of HIV ($EC_{90\ ADA}$ = 0.75 μM, 452 ng/ml and $EC_{90\ DGV}$ = 0.3 μM, 180 ng/ml) and at inhibiting the extracellular accumulation of the p24 capsid protein from H-9 cells chronically infected with HIV-1 IIIB (EC_{50} of 0.39 μM [235 ng/ml] and EC_{90} of 1.90 μM [1144 ng/ml]). These concentrations are below the 50% cellular toxicity concentration range of 7-35 μM (4218-21093 ng/ml) of tipranavir. Protein binding studies have shown that the antiviral activity of tipranavir decreases on average 3.75-fold in conditions where human serum is present. When used in combination with other antiretrovirals, tipranavir shows synergy to additivity with the NRTI zidovudine, and the protease inhibitor ritonavir. Activities ranging from synergy to antagonism were reported when tipranavir was used in combination with the protease inhibitors lopinavir and amprenavir.

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 24-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 eight 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 APTIVUS 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.

Clinical pharmacodynamic data: The following clinical data is derived from analyses of 24-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 APTIVUS co-administered with low dose ritonavir (500 mg/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 APTIVUS/ritonavir in a separate roll-over study.

The 1159 patients included in the primary interim analysis had a median age of 43.0 years (range 17-80), were 88 % male, 73 % white, 14 % black and 1 % Asian. In the APTIVUS and comparator arms median baseline CD4 cell counts were 155 and 158 cells/mm^3, respectively, (ranges 1-1893 and 1-1184 cells/mm^3); median baseline plasma HIV-1 RNA was 4.83 and 4.82 $\log_{10}$ 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 19% were possibly resistant to the pre-selected comparator PIs. A total of 12% of patients had previously used enfuvirtide. Patients had baseline HIV-1 isolates with an average 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, 20% had mutations at codons 82 (less than 2% of patients had the mutation V82L) and 90, 15% had mutations at codons 84 and 90 and 50% had at least one key mutation at codon 90. One patient in the APTIVUS 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 treatment response (composite endpoint defined as patients with a confirmed $\geq$1 log RNA drop from baseline and without evidence of treatment failure) for both studies was 41% in the APTIVUS/ritonavir arm and 19% 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 24 (pooled studies RESIST-1 and RESIST-2 in treatment-experienced patients)

RESIST study	APTIVUS/RTV		CPI/RTV**		p-value
	n (%)	N	n (%)	N	
Overall population					
FAS	240 (41.2)	582	109 (18.9)	577	<0.0001
PP	166 (44.7)	371	81 (22.5)	360	<0.0001
- with ENF (FAS)	92 (58.2)	158	33 (25.8)	128	<0.0001
- without ENF (FAS)	148 (34.9)	424	76 (16.9)	449	<0.0001
Genotypically Resistant					
LPV/rtv					
FAS	69 (36.9)	187	29 (14.6)	199	<0.0001
PP	46 (39.0)	118	20 (16.3)	123	<0.0001
APV/rtv					
FAS	48 (42.9)	112	21 (17.9)	117	<0.0001
PP	37 (45.7)	81	14 (18.7)	75	0.0003
SQV/rtv					
FAS	30 (52.6)	57	9 (17.0)	53	<0.0001
PP	18 (51.4)	35	3 (12.0)	25	0.0002
IDV/rtv					
FAS	8 (61.5)	13	1 (6.3)	16	0.0005
PP	4 (66.7)	6	1 (7.7)	13	0.0046

* 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 400/100 mg bid (n=290), IDV/r 800/100 mg bid (n=20), SQV/r 1000/100 mg bid or 800/200 mg bid (n=118), APV/r 600/100 mg bid (n=149)

Through 24 weeks of treatment, the proportion of patients in the APTIVUS/ritonavir arm compared to the comparator PI/ritonavir arm with HIV-1 RNA < 400 copies/ml was 34% and 16% respectively, and with HIV-1 RNA < 50 copies/ml was 23% and 9% respectively. Among all randomised and treated patients, the median change from baseline in HIV-1 RNA at the last measurement up to Week 24 was -0.80 $\log_{10}$ copies/ml in patients receiving APTIVUS/ritonavir versus -0.25 $\log_{10}$ 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 24 was +34 cells/mm^3 in patients receiving APTIVUS/ritonavir (N=582) versus +4 cells/mm^3 in the comparator PI/ritonavir (N=577) arm.

The superiority of APTIVUS co-administered with low dose ritonavir over the comparator protease inhibitor/ritonavir arm was observed for all efficacy parameters at week 24. It has not been shown that APTIVUS is superior to these boosted comparator protease inhibitors in patients harbouring strains susceptible to these protease inhibitors. RESIST data also demonstrate that APTIVUS co-administered with low dose ritonavir exhibits a better treatment response at 24 weeks when the OBR contains genotypically available antiretroviral agents (eg enfuvirtide).

These studies are currently continuing and longer term data will be supplied when available. At present there are no results from controlled trials evaluating the effect of APTIVUS on clinical progression of HIV.

Analyses of tipranavir resistance in treatment experienced patients

Analyses were also conducted to assess virologic 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 in the RESIST Phase III studies. Response rates were reduced if five or more primary PI mutations were present at baseline and subjects did not receive concomitant enfuvirtide (ENF) with APTIVUS.

The median change from baseline in HIV-1 RNA at weeks 2, 4, 8, 16 and 24 was evaluated by the number of baseline primary PI mutations (1-4 or $\geq$ 5) in subjects who received APTIVUS, co-administered with low dose ritonavir, with or without enfuvirtide. The following observations were made:

- Approximately 1.5 $\log_{10}$ decrease in HIV-1 RNA occurs at early time points (week 2) regardless of the number of baseline primary PI mutations (1-4 or 5+)

- Subjects with 5 or more primary PI mutations in their HIV-1 at baseline who received APTIVUS/ritonavir without enfuvirtide began to lose antiviral activity between Weeks 4 and 8

- Sustained HIV-1 RNA decreases (1.5 – 2 $\log_{10}$) through Week 24 were observed in subjects with 5 or more primary PI mutations at baseline who received APTIVUS/ritonavir and enfuvirtide.

Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change pending additional data.

APTIVUS/ritonavir response rates were assessed by baseline tipranavir genotype and phenotype. Relationships between baseline phenotypic susceptibility to tipranavir, mutations at amino acids 33, 82, 84 and 90, tipranavir resistance-associated mutations, and response to APTIVUS/ritonavir therapy at week 24 were assessed (see table below).

At 24-weeks, a higher proportion of patients receiving APTIVUS, co-administered with low dose ritonavir, achieved a treatment response in comparison to the comparator protease inhibitor/ritonavir for nearly all of the possible combinations of baseline mutations at positions 33, 82, 84 or 90. However, mutations at three of these positions resulted in reduced susceptibility to APTIVUS/ritonavir and four mutations resulted in resistance.

Virologic response to APTIVUS/ritonavir therapy has been evaluated with respect to baseline genotype in treatment experienced patients participating in trials RESIST-1 and RESIST-2. A score (counting the 16 amino acids that have been associated with reduced tipranavir susceptibility and/or reduced 24-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) was applied to baseline viral protease sequences. A correlation between the tipranavir susceptibility score and response to APTIVUS/ritonavir therapy at weeks 2 and 24 has

been established. At week 2 viral load responses of ≥1.25 $\log_{10}$ were seen in patients whose viruses had less than 8 tipranavir-associated mutations. Viral load responses at week 24 were decreased as the number of tipranavir-associated mutations increased.

HIV RNA response by baseline tipranavir phenotype in the RESIST-1 and RESIST-2 trials

Baseline TPV phenotype (Fold Change)	Proportion of responders* with no ENF use	Proportion of responders* with ENF use	No. of baseline protease mutations at 33, 82, 84, 90	No. of baseline TPV resistance-associated mutations**	TPV susceptibility
0-3	45% (74/163)	77% (46/60)	**0-2**	**0-4**	Susceptible
>3-10	21% (10/47)	43% (12/28)	**3**	**5-7**	Decreased Susceptibility
>10	0% (0/8)	57% (4/7)	**4**	**8+**	Resistant

*Confirmed ≥ 1 $\log_{10}$ decrease at Week 24
**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

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 (Pgp) 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 $AUC_{0\text{-}12h}$, C_{max} and C_{min} and decreases the clearance of tipranavir. Tipranavir co-administered with low dose ritonavir (500 mg/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 Pgp substrate, a weak Pgp inhibitor and appears to be a potent Pgp inducer as well. Data suggest that, although ritonavir is a Pgp inhibitor, the net effect of APTIVUS, co-administered with low dose ritonavir, at the proposed dose regimen at steady-state, is Pgp 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 500 mg 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/ritonavir. Therefore APTIVUS, co-administered with low dose ritonavir, should be given with food. Data are awaited to substantiate the influence of food on oral absorption.

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 drug concentration over this concentration range.

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

Metabolism: *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 drug 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 (^{14}C-tipranavir/ritonavir, 500 mg/200 mg 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 tipranavir/ritonavir 500 mg/200 mg 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/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 elderly 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/ritonavir (500 mg/200 mg 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 dysfunction: 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 dysfunction: 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. APTIVUS is contraindicated in moderate or severe hepatic impairment (see sections 4.2 and 4.3).

Paediatrics: The pharmacokinetic profile of tipranavir in paediatric patients has not been established.

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) and activated partial thromboplastin time (APTT). 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 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 drug 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.

Long term animal carcinogenicity bioassays are currently in progress. However, 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.

6.4 Special precautions for storage

Store in a refrigerator (+2 to +8°C).

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.

6.5 Nature and contents of container

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

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER(S)

EU/1/05/315/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 October 2005

10 DATE OF REVISION OF THE TEXT

LEGAL CATEGORY
POM

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What APTIVUS is and what it is used for
2. Before you take APTIVUS
3. How to take APTIVUS
4. Possible side effects
5 Storing APTIVUS
6. Further information

APTIVUS 250 mg Soft Capsules
Tipranavir

- 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.

The Marketing Authorisation Holder is:

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

The Manufacturer is:

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

1. WHAT APTIVUS IS AND WHAT IT IS USED FOR

The active substance tipranavir is an antiretroviral agent used in the treatment of Human Immunodeficiency Virus (HIV) infection. Tipranavir belongs to a group of medicines called protease inhibitors. Tipranavir is an inhibitor of the HIV protease enzyme which the HIV needs to multiply. By inhibiting the protease enzyme APTIVUS helps control HIV infection. APTIVUS is prescribed for use in combination with low dose ritonavir and other antiretrovirals.

Because APTIVUS is specifically used for the treatment of HIV which is resistant to most other antiretrovirals, your doctor will take blood samples before starting treatment to test that the HIV in your blood is resistant and that APTIVUS treatment is appropriate.

APTIVUS capsules are pink coloured, 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.

2. BEFORE YOU TAKE APTIVUS

Aptivus is to be taken in combination with low dose ritonavir and other antiretroviral medicines. It is therefore important that you carefully read the Package Leaflet that is provided with these medicines. If you have any further questions about ritonavir or the other medicines prescribed, please ask your doctor or pharmacist.

Do not take APTIVUS:
- if you are hypersensitive (allergic) to tipranavir or any of the other ingredients of APTIVUS
- if you are currently taking rifampicin (used to treat tuberculosis) as this may stop APTIVUS from working properly
- if you have moderate to severe liver problems. In addition your doctor, based upon blood tests used to monitor your liver function, may decide to delay the start, or to stop APTIVUS therapy
- if you are currently taking products containing cisapride (used to treat stomach problems), pimozide or sertindole (used to treat schizophrenia), triazolam (used to treat anxiety or sleep disorders), ergot derivatives (used to treat headaches), astemizole or terfenadine (used to treat allergies or hay fever), the statins simvastatin or lovastatin (used to lower blood cholesterol) or amioradone, bepridil, flecainide, propafenone or quinidine (used to treat heart disorders).

Patients taking APTIVUS must not take products containing St John's wort (*Hypericum perforatum*) as this may stop APTIVUS from working properly.

Take special care with APTIVUS:
- APTIVUS may interact with other medicines, which may lead to dangerous side-effects. These include erectile dysfunction agents (eg sildenafil, vardenafil, tadalafil), agents to treat alcohol dependence (disulfiram), anti-asthma agents (fluticasone), lipid lowering agents (atorvastatin) and agents to treat infections (metronidazole). You must tell your doctor about all medicines which you are taking, or planning to take, including those medicines you can buy without a prescription.
- APTIVUS may also interact with other types of medicines, which may lead to a loss of effectiveness of these medicines. These include the morphine-substitute methadone and oral contraceptives. If you are using oral contraceptives to prevent pregnancy you should use an additional or different type of contraception.
- if you have liver disease or hepatitis. Patients with higher liver function tests and patients with hepatitis B or C infection are at increased risk for severe and potentially fatal liver damage while taking antiretroviral therapy in general, including APTIVUS. Your doctor will monitor the function of your liver by blood tests before and during APTIVUS treatment. If you have liver disease or hepatitis your doctor will decide if you need additional testing. If you notice the signs or symptoms of hepatitis (fever, malaise, nausea, vomiting, abdominal pain, fatigue, jaundice) you should inform your doctor as soon as possible.
- if you have type A or B haemophilia
- if you have diabetes
- mild to moderate rash, including flat or raised rashes or sensitivity to the sun, have been reported in approximately 10% of subjects receiving APTIVUS. Some patients who developed rash also had joint pain or stiffness, throat tightness, or generalized itching.
- always take APTIVUS together with ritonavir, as failure to take ritonavir will prevent APTIVUS from working properly.

APTIVUS is not a cure for HIV infection and 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. In addition, APTIVUS does not prevent the risk of transmission of HIV to

others through blood or sexual contact. You should therefore continue to use appropriate precautions to prevent this.

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 the levels of blood lipids (fats) both 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, please inform your doctor immediately.

Aptivus should not be used by patients under 18 years of age.

Taking APTIVUS with food and drink:
APTIVUS should be taken with food.

Pregnancy
Tell your doctor if you are pregnant or planning to become pregnant. If you are pregnant APTIVUS should only be taken after careful discussion with your doctor. The safe use of APTIVUS in pregnancy has not been established.

APTIVUS contains very small amounts of alcohol (see *Important information about some of the ingredients of APTIVUS*). Tell your doctor immediately if you become pregnant.

Ask your doctor or pharmacist for advice before taking any medicine.

APTIVUS can affect oral contraceptives (see 2. Taking other medicines). Therefore, you should employ an alternative, effective and safe contraceptive method if you are taking APTIVUS.

Breast-feeding:
Make sure you tell your doctor if you are breast-feeding. APTIVUS contains very small amounts of alcohol (see *Important information about some of the ingredients of APTIVUS*). It is anyway recommended that HIV-infected women must not breast-feed babies because it is possible that the baby can become HIV-infected through the breast milk.

Driving and using machines:
APTIVUS has not been tested for its effect on your ability to drive a car or operate machinery. APTIVUS contains very small amounts of alcohol (see *Important information about some of the ingredients of APTIVUS*).

Important information about some of the ingredients of APTIVUS:
APTIVUS contains 7 % ethanol (alcohol), ie up to 200 mg per dose, equivalent to 4 ml of beer, or less than 2 ml of wine.

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

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

Taking other medicines:

Before starting treatment with APTIVUS, please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed. This is **very important**, as taking

some types of medicines at the same time with APTIVUS and ritonavir can strengthen or weaken the effect of the medicines. This can sometimes lead to serious medical conditions.

APTIVUS, taken together with ritonavir, may interact with other medicines. Your doctor may have to increase or decrease the dose of other medicines which you take together with APTIVUS. Examples include the cholesterol-reducing agent atorvastatin, the antibiotics rifabutin and clarithromycin, the asthma treatment theophylline and the antidepressant desipramine.

In addition, medicines containing rifampicin (antibiotic) and St. John's wort are likely to prevent APTIVUS from working properly and should not be taken together with APTIVUS (see *2. BEFORE YOU TAKE APTIVUS*).

If you are taking didanosine enteric coated tablets, it should be separated by at least two hours from APTIVUS.

Your doctor will only prescribe you abacavir and zidovudine if you are unable to take other nucleoside reverse transcriptase inhibitors. Otherwise, APTIVUS, taken together with ritonavir, can be taken together with the HIV reverse transcriptase inhibitors stavudine, lamivudine, or tenofovir.

Your doctor will use caution if you have to take concomitant non nucleoside reverse transcriptase inhibitors (efavirenz or nevirapine) because there is currently limited data on the use of these medicines with APTIVUS taken with ritonavir.

APTIVUS, taken together with ritonavir, strongly decreases the blood levels of the HIV protease inhibitors amprenavir, lopinavir and saquinavir. Your doctor will carefully consider whether to treat you with combinations of APTIVUS and these protease inhibitors.

APTIVUS, taken together with ritonavir, can affect oral contraceptives and therefore you should employ an alternative contraceptive method such as barrier contraception (eg condoms) if you are taking APTIVUS. 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, but you should talk to your doctor as you may need to temporarily stop taking either APTIVUS or the other medicine that contains oestrogen or female hormones.

3. HOW TO TAKE APTIVUS

Always take APTIVUS exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. It is essential that you take APTIVUS together with ritonavir. The usual dose is 500 mg (two 250 mg capsules) APTIVUS, together with 200 mg (two 100 mg capsules) ritonavir, twice per day with food. The capsules should always be taken by mouth, and swallowed whole and not chewed. APTIVUS will also always be taken in combination with other antiretroviral medicines, for which you should follow the instructions within the supplied Package Leaflet.

You should continue to take APTIVUS for as long as instructed by your doctor.

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

If you forget to take APTIVUS:
Take the next dose of APTIVUS, together with ritonavir, as soon as possible. Do not take a double dose to make up for forgotten individual doses.

Effects when treatment with APTIVUS is stopped:
It has been shown that taking all doses at the appropriate times may greatly increase the effectiveness of your combination antiretroviral medicines and reduce the chances of development of antiretroviral resistance. Therefore, unless your doctor instructs you to stop treatment, it is important to keep taking APTIVUS correctly, as described above.

4. POSSIBLE SIDE EFFECTS

Like all medicines, APTIVUS can have side effects. It may be difficult to tell between side effects caused by APTIVUS, by the other medicines you are also taking, or by the complications of HIV infection. For this reason it is very important that you tell your doctor about any changes in your health.

Very common side effects (which can occur in more than one in 10 patients treated) are diarrhoea and nausea. Common side effects (which can occur in less than one in ten but in more than one in a hundred patients treated) are vomiting, abdominal pain, flatulence, tiredness, headache and rash.

The most commonly reported changes in blood chemistry are increases in blood lipid (fat) levels (very common) and increases in liver enzyme activity (common).

Uncommon side effects (which can occur in less than one in a hundred but more than one in a thousand patients treated) are reduction in red and white blood cells, reduction in blood platelets, allergic reactions, decreased appetite, diabetes, increased blood levels of the pancreas enzyme amylase, increased cholesterol blood levels, sleeplessness and other sleep disorders (including sleepiness), dizziness, numbness and/or tingling and/or pain in the feet or hands, breathing difficulties, heartburn, inflammation of the pancreas, skin inflammation, loss or gain of body fat and other changes in fat distribution (see below), muscle cramp, muscle pain, kidney malfunction, flu like symptoms, general feelings of illness, fever and weight loss.

Rare side effects (which can occur in less than one in a thousand patients treated) are dehydration, thinning of the face, increased blood sugar and increased blood levels of the pancreas enzyme lipase.

Abnormal liver function has been reported with the use of APTIVUS. This has included uncommon reports of hepatitis (which can occur in less than one in a hundred patients treated) and rare reports of liver failure (which can occur in less than one in a thousand patients treated), including fatal outcome.

If you experience clinical symptoms suggesting an injury of the liver, such as loss of appetite, nausea, vomiting and/or jaundice, you should inform your doctor.

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. Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipidaemia (increased fats in the blood) and resistance to insulin.

In patients with haemophilia type A and B, there have been reports of increased bleeding while taking this treatment or another protease inhibitor. Should this happen to you, seek immediate advice from your doctor.

Bleeding in the brain, which can lead to permanent disability or death, has occurred in some patients treated with APTIVUS in clinical trials. A majority of the patients experiencing intracranial haemorrhage (ICH) in the APTIVUS clinical development programme had other medical conditions or were receiving concomitant medications that may have caused or contributed to these events.

There have been reports of muscle pain, tenderness or weakness, particularly in combination antiretroviral therapy including protease inhibitors and nucleoside analogues. On rare occasions these muscle disorders have been serious (rhabdomyolysis).

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING APTIVUS

Keep out of the reach and sight of children.

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 use after the expiry date stated on the bottle.

Medicines no longer required should not be disposed of via wastewater or the municipal drainage system. Return them to a pharmacy or ask your pharmacist how to dispose of them in accordance with the national regulations. These measures will help to protect the environment.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
n.v. Boehringer Ingelheim s.a.
Tél/Tel: +32 2 773 33 11

Ceská republika
Boehringer Ingelheim spol. s r.o.
Tel: +420 234 655 111

Danmark
Boehringer Ingelheim Danmark A/S
Tlf: +45 39 15 88 49

Deutschland
Boehringer Ingelheim Pharma GmbH & Co. KG
Tel: +49 1805 / 77 90 90

Eesti
Boehringer Ingelheim Pharma GmbH
Eesti Filiaal
Tel: +372 60 80 940

E???da
Boehringer Ingelheim Ellas A.E.
T??: +30 2 10 89 06 300

España
Boehringer Ingelheim España S.A.
Tel: +34 93 404 58 00

France
Boehringer Ingelheim France S.A.S.
Tél: +33 3 26 50 45 33

Ireland
Boehringer Ingelheim Ireland Ltd.
Tel: +353 1 295 9620

Ísland
Vistor hf.
Tel: +354 535 7000

Italia
Boehringer Ingelheim Italia S.p.A.
Tel: +39 02 5355 1

? ?p???
Boehringer Ingelheim Ellas A.E.
T??: +30 2 10 89 06 300

Latvija
Boehringer Ingelheim Pharma GmbH
Parstavnieciba Latvija
Tel: +371 7 240 068

Luxembourg/Luxemburg
n.v. Boehringer Ingelheim s.a.
Tél/Tel: +32 2 773 33 11

Magyarország
Boehringer Ingelheim Pharma Fióktelep
Tel.: +36 1 224 7120

Malta
Boehringer Ingelheim Ltd.
Tel: +44 1344 424 600

Nederland
Boehringer Ingelheim b.v.
Tel: +31 72 5 66 24 24

Norge
Boehringer Ingelheim Norway KS
Tlf: +47 66 76 13 00

Österreich
Boehringer Ingelheim Austria GmbH
Tel: +43 1 80 105-0

Polska
Boehringer Ingelheim Sp.zo.o.
Tel.: +48 22 699 0 699

Portugal
Boehringer Ingelheim, Lda.
Tel: +351 21 313 53 00

Slovenija
Boehringer Ingelheim Pharma
Podru nica Ljubljana
Tel: +386 1 586 40 00

Slovenská republika
Boehringer Ingelheim Pharma
organizacná zlo ka
Tel: +421 2 5810 1211

Suomi/Finland
Boehringer Ingelheim Finland Ky
Puh/Tel: +358 10 3102 800

Sverige
Boehringer Ingelheim AB
Tel: +46 8 721 21 00

United Kingdom
Boehringer Ingelheim Ltd.
Tel: +44 1344 424 600

Lietuva
Boehringer Ingelheim Pharma Ges mbH
Atstovybe Lietuvoje
Tel.: +370 37 473922

This leaflet was last approved on (MM/YYYY)