ADIS DRUG PROFILE

Drugs 2003; 63 (15): 1611-1618
0012-6667/03/0015-1611/$33.00/0

Tipranavir

Greg L. Plosker and *David P. Figgitt*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ Tipranavir is a potent and selective non-peptidic HIV-1 protease inhibitor with a markedly improved resistance profile compared with traditional, peptidomimetic protease inhibitors.

▲ The presence of five or fewer protease gene mutations or one or two protease inhibitor resistance-associated mutations (PRAMs) is associated with reduced susceptibility to currently available protease inhibitors. However, 16–20 mutations (including three or more PRAMs) may be needed to confer resistance to tipranavir.

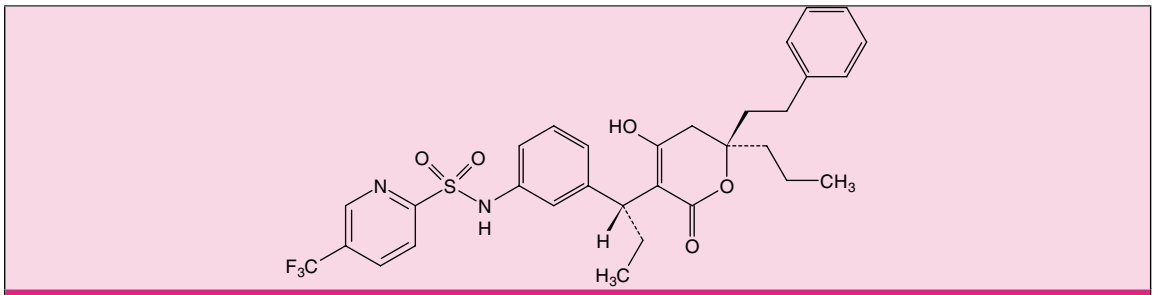
▲ Tipranavir-based therapy achieved sustained viral suppression for more than 48 weeks in a small phase II trial in multiple protease inhibitor-experienced HIV-infected patients.

▲ A large dose-finding study demonstrated potent virological reduction through 14 days of functional monotherapy in heavily pretreated HIV-infected patients with 6 to >20 protease gene mutations at baseline.

▲ Two large, ongoing, phase III trials in patients with multi-drug resistant HIV infection are comparing the efficacy of tipranavir/ritonavir 500/200mg twice daily plus a patient-individualised background antiretroviral regimen versus other ritonavir-boosted protease inhibitor regimens.

▲ In general, tipranavir has been well tolerated in clinical trials. As with other protease inhibitors, the most common adverse events with tipranavir have been gastrointestinal disturbances.

Features and properties of tipranavir (PNU-140690)	
Indication	
HIV infection	
Mechanism of action	
Antiviral	Non-peptidic protease inhibitor
Dosage and administration	
Usual dosage in clinical trials	Tipranavir 500mg/ritonavir 200mg
Route of administration	Oral
Frequency of administration	Twice daily
Pharmacokinetic profile of tipranavir after oral administration of tipranavir/ritonavir 500/200mg twice daily for 7 days in protease inhibitor-experienced patients with HIV infection (median values)	
Trough plasma concentration	32.1 μmol/L
Peak plasma concentration	≈80 μmol/L (estimated from graph)
Time to peak plasma concentration	≈1.5–2h (estimated from graph)
Time to steady state	≤7 days
Adverse events	
Main events	Gastrointestinal complaints (primarily diarrhoea, nausea, vomiting)



Tipranavir

Tipranavir is the first non-peptidic protease inhibitor in development for the treatment of patients with HIV infection.[1] Data from *in vitro* studies and phase II clinical trials indicate that the drug has a robust resistance profile and potentially durable effects on viral load suppression in heavily pretreated patients. Large, ongoing, phase III trials are comparing the efficacy of tipranavir-based regimens with other protease inhibitor-based regimens as salvage therapy in patients with extensive antiretroviral experience.[2]

Tipranavir is used as part of orally administered multiple-drug therapy in combination with nucleoside reverse transcriptase inhibitors (NRTIs) and/or non-nucleoside reverse transcriptase inhibitors (NNRTIs). Like traditional (peptidomimetic) protease inhibitors such as saquinavir[3] and lopinavir,[4] tipranavir is administered in regimens 'boosted' by subtherapeutic doses of ritonavir,[5] a potent inhibitor of cytochrome P450 (CYP) 3A4[6] and the efflux transporter P-glycoprotein (P-gp).[7] Since protease inhibitors are extensively metabolised by CYP3A4[8] and are P-gp substrates (P-gp expressed in the gut wall may limit protease inhibitor uptake),[7] this boosting or pharmacoenhancement results in a marked increase in systemic exposure of tipranavir or other protease inhibitors boosted by ritonavir.[7,9] Ritonavir-boosted tipranavir regimens are denoted as TPV/r throughout this article.

1. Pharmacodynamic Profile

Human HIV protease is a proteolytic enzyme necessary for activation of viral polyprotein precursors into functional proteins.[10] Exposure of HIV-infected cells to protease inhibitors results in the formation of immature, noninfectious virus particles. However, the emergence of drug resistance during antiretroviral therapy directed at specific HIV enzymatic targets (i.e. HIV-1 protease or reverse transcriptase) remains an important clinical limitation of protease inhibitors as well as NRTIs and NNRTIs.[10]

Although more than 20 possible amino acid substitutions in the HIV-1 protease have been identified during protease inhibitor therapy,[10] the primary protease gene mutations that confer resistance to protease inhibitors are L33I/V/F, V82A/F/L/T, I84V and L90M.[11,12] These are sometimes referred to as protease inhibitor resistance-associated mutations (PRAMs). However, resistance to protease inhibitors is dependent upon both the specific mutations present and the number of mutations present.[10,13] The presence of one or two PRAMs is associated with reduced susceptibility to all currently marketed protease inhibitors.[14] Likewise, currently marketed protease inhibitors may be rendered ineffective by five or fewer mutations in the virus.[15,16]

- Crystal structure evaluation indicates that tipranavir binds to the active site of HIV-1 protease.[1] This is supported by enzymatic data showing that the drug has high potency and selectivity for HIV-1 protease (K_i < 0.01 nmol/L vs HIV-1 protease, K_i <1 nmol/L vs HIV-2 protease).[1]
- *In vitro* data indicate that most clinical isolates of HIV that are highly resistant to traditional, peptidomimetic protease inhibitors remain susceptible to tipranavir.[12,17-19] For example, among 105 clin-

ical isolates with broad cross-resistance to protease inhibitors (>10-fold increase in 50% inhibitory concentration [IC_{50}] to at least three of the protease inhibitors indinavir, ritonavir, saquinavir and nelfinavir), 90% were sensitive to tipranavir.[12] This lack of cross-resistance is not yet explained on a molecular level.

- Wild-type HIV-1 passaged in the presence of ritonavir [HIV-1_{NL4-3} (p37)] exhibited profound resistance to traditional protease inhibitors, whereas a relatively small increase in resistance to tipranavir was observed.[1] Compared with the parent strain, HIV-1_{NL4-3} (p37) was 80-fold more resistant to ritonavir, 47-fold more resistant to indinavir, ≥125-fold more resistant to nelfinavir and saquinavir, but only 6.5-fold more resistant to tipranavir.[1] When wild-type HIV was passaged for several months in the presence of increasing concentrations of tipranavir, the development of five or more of the mutations L33F, I84V, V82L, K45I and I13V/V32I in the replicating virus population conferred a marked reduction in susceptibility to tipranavir (and various marketed protease inhibitors).[20]

- *In vitro* data indicate that the combination of tipranavir and ritonavir results in additive to moderately synergistic antiviral activity against a ritonavir-sensitive HIV-1 clinical isolate and stronger synergy versus a ritonavir-resistant isolate.[21] Additive to synergistic antiviral effects were also demonstrated *in vitro* when tipranavir was combined with zidovudine or delaviridine,[1] and an additive effect was noted when tipranavir and lopinavir were combined.[22]

- Evaluation of clinical isolates of HIV-1 from protease inhibitor-experienced patients enrolled in phase II clinical trials has shown that as many as 16–20 protease gene mutations[14,23-25] (including three or more PRAMs[14,24]) are needed to confer resistance to tipranavir, whereas relatively few mutations result in HIV resistance to traditional, peptidomimetic protease inhibitors.[15,16] For example, evaluation of 177 clinical isolates from patients in the BI 1182.52 trial (described in section 3) showed that the median fold change in IC_{50} (relative to wild-type HIV) for available protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir) ranged from 4.9–31.9 in the presence of one PRAM, 9.6–97.9 with two PRAMs, and 17.1–422 with three PRAMs.[14] In contrast, the presence of one, two or three PRAMs resulted in 1-, 1.3- and 2.2-fold increases in wild-type IC_{50} for tipranavir.

- The apparent breakpoint in susceptibility to tipranavir was approximately a 2-fold increase in wild-type IC_{50} in the clinical isolates from patients in the BI 1182.52 trial.[14] At the end of 2 weeks of functional monotherapy with various regimens of TPV/r (plus NRTIs and/or NNRTIs from the previous/failing regimen), median reductions in viral load were 1.23 and 1.24 log_{10} copies/mL with ≤1-fold and 1–2-fold increases in wild-type IC_{50}, respectively, compared with reductions of only 0.21 and 0.19 log_{10} copies/mL with >2–4-fold and >4-fold increases. Less than one-third of the isolates (30.6%) showed a >2-fold increase in wild-type IC_{50} and these had large numbers of protease gene mutations. Therefore, baseline phenotypic susceptibility to tipranavir was maintained in the majority of clinical isolates (60.4%), most of which were highly resistant to traditional protease inhibitors.

2. Pharmacokinetic Profile

During the phase II trial known as BI 1182.2 in 41 protease inhibitor-experienced patients, the tipranavir formulation used in the study was switched from the hard-gel capsule to a self-emulsifying drug delivery system (see section 3).[26] Thus, it appears that more recent pharmacokinetic data, such as those from the BI 1182.52 trial, pertain to tipranavir in the self-emulsifying drug delivery system, whereas earlier data are for the hard-gel capsule formulation. Since most available data on tipranavir have been briefly reported as abstracts, the specific oral formulation of tipranavir used in pharmacokinetic (and clinical) trials was usually not stated.

- Early studies in healthy volunteers[27] or patients with HIV infection[28] receiving non-boosted regimens of tipranavir 900–2000mg (disodium salt capsule or formulation not stated) three times daily

showed mean steady-state trough plasma concentrations of approximately 1–3 μmol/L. Clearance was somewhat higher after multiple- than single-dose regimens, thus tipranavir may induce its own metabolism by hepatic enzymes.[27]

- Pharmacokinetic interaction studies between tipranavir and ritonavir in healthy volunteers showed a significant two-way interaction resulting in a marked increase in tipranavir plasma concentrations and a reduction in ritonavir concentrations.[29] Trough plasma concentrations of tipranavir were increased by 9-fold when ritonavir 100mg twice daily was administered concurrently with tipranavir 600mg twice daily, and by 40-fold when the ritonavir dosage was increased to 500mg twice daily. Tipranavir 600–1350mg twice daily reduced trough plasma ritonavir concentrations by about 90% when administered concomitantly with ritonavir 500mg twice daily. These results supported the evaluation of TPV/r regimens in subsequent clinical trials.

- The pharmacokinetic analysis in the BI 1182.52 trial (see section 3) showed little difference in median trough concentrations of tipranavir after 7 and 14 days of TPV/r therapy, thus indicating that steady state was reached within 7 days.[30] Median trough tipranavir concentrations on day 7 were 32.1, 52.3 and 21.8 μmol/L for TPV/r 500/200, 750/200 and 500/100mg twice-daily regimens, respectively. Median peak plasma tipranavir concentration was approximately 80 μmol/L and was achieved approximately 1.5–2 hours after administration of TPV/r 500/200mg (estimated from a graph of individual pharmacokinetic data for a small subset of patients).

- Pharmacokinetic data from all 216 HIV-infected patients with extensive antiretroviral therapy in the BI 1182.52 trial showed that the median trough plasma concentrations of tipranavir exceeded the target value of 20 μmol/L (ten times the protein-adjusted IC_{90} for protease inhibitor-resistant HIV) with all three ritonavir-boosted tipranavir regimens.[30] The target concentration was achieved in a greater proportion of patients treated with the higher twice-daily dosage regimens of TPV/r 500/200mg and 750/200mg than the lower dosage regimen of 500/100mg twice daily (78%, 77% and 48%). Consistent viral suppression was achieved at trough plasma tipranavir concentrations above 15 μmol/L; some patients achieved virological response with lower concentrations.

- The inhibitory quotient (IQ) of tipranavir was >25 in 82.8% and >50 in 66.9% of a subset of 157 patients in the BI 1182.52 study.[31] IQ was determined during the first 2 weeks of functional monotherapy with twice-daily TPV/r by dividing the mean trough plasma tipranavir concentration by the protein-adjusted IC_{50}. Viral load reductions were relatively low for IQs of ≤25 and an apparent IQ breakpoint of 25–50 was observed (figure 1). These results suggest that a durable virological response is feasible with boosted tipranavir regimens.

- Results of drug interaction studies in healthy volunteers indicate that, despite modest and often statistically significant effects on various pharmacokinetic parameters, dosage adjustments are not necessary when TPV/r regimens are administered concurrently with nevirapine,[32] efavirenz, zidovudine, didanosine or tenofovir.[5] However, administration of enteric-coated didanosine and TPV/r should be separated by ≥4 hours.[5]

- Food increases the systemic absorption of non-boosted tipranavir administered as a single dose of 900mg (hard-gel capsules); area under the plasma concentration-time curve (AUC) approximately doubled compared with the fasting state ($p = 0.0001$), peak plasma drug concentration (C_{max}) increased by 55% ($p = 0.0001$) and time to achieve C_{max} increased by approximately 1 hour ($p = 0.02$).[33] AUC and C_{max} were 33% (not statistically significant) and 41% ($p = 0.015$) lower when tipranavir was taken with antacid than without antacid in the fasting state. Tipranavir may be taken with food for improved tolerability.

3. Therapeutic Trials

Most phase II trials with ritonavir-boosted regimens of tipranavir have been nonblind, randomised, dose-finding or small comparative studies in HIV-infected adult patients with extensive antiretroviral experience. Large, comparative, phase III trials are currently underway in heavily pretreated patients

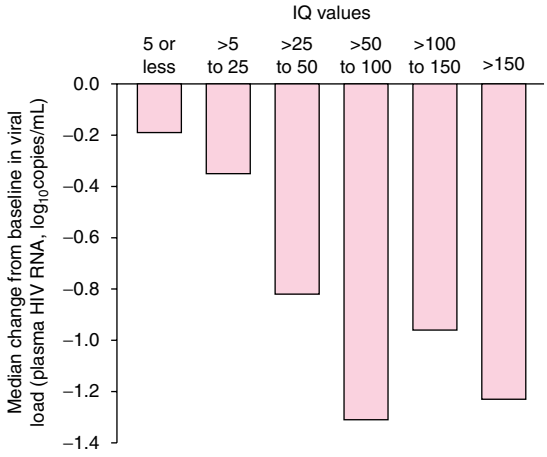


Fig. 1. Relationship between inhibitory quotient (IQ) of ritonavir-boosted tipranavir (TPV/r) and viral load suppression in 157 heavily pretreated patients with HIV infection.[31] This subgroup analysis included >70% of patients enrolled in the multicentre randomised trial BI 1182.52 in which patients received twice-daily TPV/r 500/100mg, 500/200mg or 750/200mg as functional monotherapy (including reverse transcriptase inhibitors from the previous/failing regimen) for 2 weeks.

with multi-drug resistant HIV infection. To date, all clinical trials with tipranavir have evaluated intermediate or surrogate markers of clinical efficacy in HIV disease. Studies have shown few treatment-related serious adverse events and no treatment-related deaths.

- Sustained viral suppression was demonstrated with more than 48 weeks of tipranavir-based therapy in 41 NNRTI-naive patients with HIV infection who had clinically failed two or more protease inhibitor-containing regimens.[23,26,34] In this study, known as BI 1182.2, patients were randomised to receive either TPV/r 500/100 or 1000/200mg twice daily plus efavirenz 600mg once daily and one new NRTI. Median viral load reductions for the low- (n = 19) and high-dose (n = 22) groups were 1.67 and 2.34 $\log_{10}$ copies/mL, respectively, and corresponding mean increases in CD4+ cell counts were 184 and 149 cells/μL. In the intention-to-treat (ITT) analysis at 48 weeks, 79% and 50% of patients in the low- and high-dose groups had plasma HIV RNA levels below 400 copies/mL; 68% and 41% of patients had an undetectable viral load when the limit of detection was 50 copies/mL. Results of the per-protocol analysis are presented in figure 2.

- Short-term antiviral activity was demonstrated with various ritonavir-boosted regimens of tipranavir (TPV/r 500/100, 500/200 and 750/200mg twice daily) in 216 heavily pretreated HIV-infected patients with 6 to >20 protease gene mutations at baseline.[11,14,35] Entry criteria included previous treatment with all three antiretroviral drug classes including two or more protease inhibitors. Plasma HIV RNA levels decreased by 0.91–1.19 $\log_{10}$ copies/mL after 2 weeks of functional monotherapy in this randomised trial (BI 1182.52) [figure 3].[11] During the 2-week functional monotherapy period patients remained on NRTIs and/or NNRTIs from their previous/failing regimen.[14] In patients with >20 protease gene mutations (figure 3) and two or more PRAMs there was a trend toward a greater reduction in viral load with the two higher dosage regimens of TPV/r.[11] Both TPV/r 500/200 and 750/200mg twice daily were active against HIV resistant

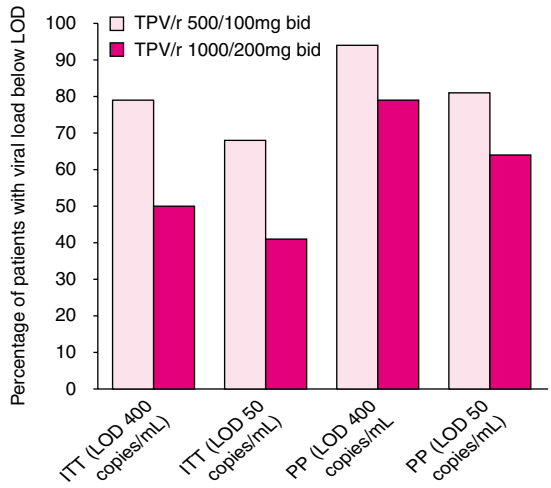


Fig. 2. Virological response to ritonavir-boosted tipranavir (TPV/r) regimens in the BI 1182.2 trial.[23,26,34] NNRTI-naive patients with HIV infection who had clinically failed two or more protease inhibitor regimens were randomised to receive a twice-daily (bid) regimen of low- (n = 19) or high-dose (n = 22) TPV/r plus efavirenz 600mg once daily and a new NRTI. Results are for the intention-to-treat (ITT) and per-protocol (PP) analyses at 48 weeks. **LOD** = limit of detection; **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **NRTI** = nucleoside reverse transcriptase inhibitor.

to all traditional protease inhibitors (see section 1).[14]

- Tipranavir was at least as effective as saquinavir in achieving viral load reductions when used as part of ritonavir-boosted regimens in single protease inhibitor-experienced patients with HIV infection, according to interim data from the BI 1182.4 trial.[25,36] In the ITT analysis at 24 weeks, 42%, 58% and 24% of patients who were randomised to receive twice-daily regimens of TPV/r 500/100mg (n = 25), TPV/r 1250/100mg (n = 25) or saquinavir/ritonavir 400/400mg (n = 29), respectively, had viral load reductions of ≥1 $\log_{10}$ copies/mL.[25] Analysis of data at 16 weeks (n = 62) showed median reductions in viral load of 1.44, 1.79 and 1.75 $\log_{10}$ copies/mL for the low-dose TPV/r, high-dose TPV/r and saquinavir groups, and 39%, 55% and 40% of patients, respectively, had an undetectable viral load (HIV RNA levels <400 copies/mL).[36]

- Two large, ongoing, multicentre trials are comparing the clinical efficacy of a tipranavir 500mg plus ritonavir 200mg twice-daily versus other boosted protease inhibitor regimens in more than 1300 highly antiretroviral-experienced patients with multi-drug resistant HIV infection.[2] Patients will also receive optimal background antiretroviral therapy (e.g. NRTI/NNRTIs) on the basis of genotypic testing. The primary endpoints of these phase III trials known as RESIST 1 and RESIST 2 (**R**andomized **E**valuation of **S**trategic **I**ntervention in Multi-Drug Re**s**istant Patients with **T**ipranavir) are the proportion of patients with a ≥1 $\log_{10}$ copies/mL reduction in viral load at 48 weeks and the time to treatment failure.

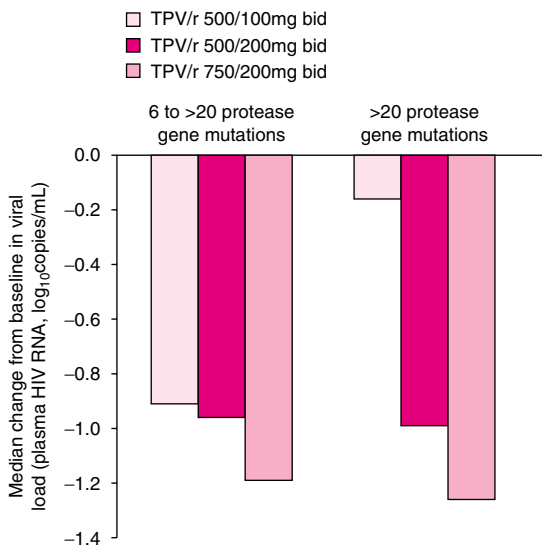


Fig. 3. Antiviral activity of twice-daily (bid) ritonavir-boosted tipranavir (TPV/r) regimens during 2 weeks of functional monotherapy in a randomised trial (BI 1182.52).[11] The study included 216 multi-drug class experienced patients with HIV infection resistant or refractory to two or more protease inhibitor-based regimens.

4. Tolerability

Tipranavir is generally well tolerated and the most common adverse events involve the gastrointestinal tract. In general, doses of ritonavir-boosted tipranavir above TPV/r 750/200mg twice daily were associated with a high incidence of diarrhoea, nausea and vomiting.[37] Ongoing phase III trials are using a lower dosage regimen of TPV/r 500/200mg twice daily.[2]

- In the 48-week trial known as BI 1182.2, 41 patients were randomised to receive either TPV/r 500/100 or 1000/200mg twice daily plus efavirenz 600mg once daily and one new NRTI. The most common adverse events thought to be associated with tipranavir were gastrointestinal, primarily diarrhoea and nausea.[26,38] Most of these events occurred during the first 2 weeks of therapy. Gastrointestinal adverse events decreased later in the trial when the tipranavir dosage formulation was switched from a hard-gel capsule to a self-emulsifying drug delivery system.[26] Most patients enrolled in the trial had hyperlipidaemia or lipodystrophy at baseline, and the study was not designed to evaluate whether tipranavir is associated with these adverse effects that are relatively common with other protease inhibitors.[38]

- After 4 weeks of therapy with TPV/r 500/100, 500/200 or 750/200mg twice daily in the BI 1182.52 trial (n = 216), 15.3% of patients experienced at least grade 2 diarrhoea and 11.6% had at least one episode of vomiting.[35] There was a dose-related trend for grade 3/4 adverse events, laboratory abnormalities and adverse events leading to treatment

discontinuation. Serious adverse events occurred in 11 patients (5.1%), and in two of the patients this was thought to be related to drug therapy.[35] The BI 1182.52 trial was designed to determine the final dose of TPV/r for phase III trials on the basis of virological response after 2 weeks of functional monotherapy (see section 3)[14] and assess tolerability after 4 weeks of treatment (during which background therapy was optimised using genotype-resistance testing).[35]

- Interim 16-week data from the BI 1182.4 trial in 62 patients showed a trend toward fewer drug-related adverse events (≥grade 2) with twice-daily TPV/r 500/100mg than TPV/r 1250/100mg or saquinavir 400mg plus ritonavir 400mg (each with two new NRTIs).[36] In the three respective treatment groups, diarrhoea occurred in 5%, 19% and 14% of patients, nausea occurred in 14%, 33% and 14% of patients, and vomiting occurred in 0%, 24% and 10% of patients. Discontinuation of therapy because of drug-related adverse events prior to 24 weeks occurred in 5%, 9.5% and 19% patients in these treatment groups.

5. Dosage and Administration

- Although formal dosage recommendations are not yet approved by regulatory authorities, studies to date support the use of TPV/r 500/200mg twice daily in combination with other antiretroviral background medications.
- This regimen of TPV/r 500/200mg twice daily was selected after a series of dose-finding studies. A retrospective analysis of preclinical, pharmacokinetic and clinical trial data indicated that TPV/r 500/100, 500/200 and 750/200mg twice daily warranted further study.[37] These regimens were evaluated as functional monotherapy in the large phase II trial BI 1182.52,[11,35] which showed somewhat greater efficacy on surrogate markers of HIV disease with the two higher dosage regimens than with the lower dosage regimen (see section 3). Since there was little difference in efficacy between the two higher dosage regimens, TPV/r 500/200mg twice daily was selected for evaluation in ongoing phase III trials.[2]

6. Tipranavir: Current Status

Tipranavir (in regimens boosted by subtherapeutic doses of ritonavir) is in late-phase clinical trials for the treatment of patients with HIV infection. Sustained viral suppression has been demonstrated for more than 48 weeks with tipranavir-based therapy in patients resistant or refractory to multiple protease inhibitor-based regimens. Evaluation of clinical isolates of HIV-1 from protease inhibitor-experienced patients has shown that as many as 16–20 protease gene mutations (including at least three PRAMs) are needed to confer resistance to tipranavir.

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Correspondence: *Greg L. Plosker*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz