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Tipranavir

A Ritonavir-Boosted Protease Inhibitor

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Abstract

▲ Tipranavir is a non-peptidic HIV-1 protease inhibitor. It binds strongly and selectively, has a favourable resistance profile, and is administered orally twice daily with a subtherapeutic dosage of ritonavir in a 'boosted' regimen (TPV/r) in order to increase its bioavailability.

▲ Analysis of clinical isolates from treatment-experienced patients identified the following tipranavir resistance-associated HIV protease mutations: L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, I84V.

▲ In two large, well designed phase III trials in protease inhibitor-experienced, HIV-infected patients, the RESIST (Randomised Evaluation of Strategic Intervention in multidrug reSistant patients with Tipranavir)-1 and -2 studies, oral TPV/r 500mg/200mg twice daily achieved a significantly better virological response after 24 weeks than standard ritonavir-boosted protease inhibitors. This held true for the proportion of patients achieving a ≥1 $\log_{10}$ decrease in plasma HIV-RNA levels (viral load) [42% and 41% vs 22% and 15%; both $p < 0.0001$; primary endpoint] and other virological parameters (the proportion of patients with undetectable viral load and total viral load reduction).

▲ In addition, a significantly larger increase in CD4+ cell count was achieved with TPV/r than comparator regimens in these trials.

▲ The most common adverse events in clinical trials of tipranavir were gastrointestinal. The incidence of treatment discontinuation because of adverse events in the RESIST trials was 8% (pooled data).

Features and properties of tipranavir (Aptivus®; PNU-140690)	
Indication	
HIV infection	
Mechanism of action	
Antiviral	Non-peptidic protease inhibitor
Dosage and administration	
Dose	Tipranavir 500mg plus ritonavir 200mg
Frequency of administration	Twice daily
Route of administration	Oral
Pharmacokinetic profile of tipranavir (after oral administration of tipranavir/ritonavir 500mg/200mg twice daily to steady state in healthy volunteers [mean values unless otherwise stated])	
Time to steady state	7–10d
Trough plasma concentration	26 μmol/L
Peak plasma concentration	129 μmol/L
Area under the plasma concentration-time curve (over dose administration interval)	934 μmol/L • h
Median elimination half-life	4h
Adverse events	
Most frequent adverse events	Gastrointestinal (including diarrhoea and nausea)
Main laboratory abnormalities	Elevations of AST, ALT, cholesterol and triglycerides

The introduction of protease inhibitors (PIs) in the mid-1990s represented an advance in the treatment of HIV infection.[1] However, as with all classes of anti-HIV drugs, resistance can be a problem,[2] and there is an ongoing need for effective new agents with robust resistance profiles, in order to maintain virological control in highly-treatment experienced patients.

Tipranavir (Aptivus®)[1] is a non-peptidic PI, and has been evaluated in patients with extensive antiretroviral experience. Like most peptidomimetic PIs (including saquinavir, indinavir, amprenavir and lopinavir), tipranavir is administered in combination with low-dose ritonavir in order to increase its systemic availability ('boosted PI').[3] Ritonavir-boosted tipranavir (TPV/r) is administered orally as part of multiple-drug therapy regimens, which also include nucleoside reverse transcriptase inhibitors (NRTIs) and/or non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Tipranavir has been reviewed previously in *Drugs*.[4] The current article reviews the pharmacology of tipranavir and the efficacy and tolerability of oral TPV/r in the treatment of adult patients with HIV infection, with the main focus being on phase III clinical trial data.

1. Pharmacological Properties

Pharmacodynamic Profile

- Tipranavir is a sulfonamide-containing dihydropyrone.[5] It binds strongly and selectively to the active site of HIV-1 protease (inhibition constant <0.01 nmol/L against HIV-1 protease and <1 nmol/L against HIV-2 protease).[5]
- *In vitro*, tipranavir suppresses viral replication of laboratory strains and clinical isolates of HIV-1, including isolates that are highly resistant to multiple peptidomimetic PIs (e.g. ritonavir, saquinavir or indinavir) and the non-peptidic PI nelfinavir.[5-7] The 90% inhibitory concentration (IC_{90}) for tipranavir against a susceptible strain of HIV-1 was 0.16 μmol/L (protein-adjusted IC_{90} of 2.0 μmol/L)[5] and against multiple-PI-resistant clinical isolates was 0.62 μmol/L.[7] Elsewhere it was indicated that the protein-adjusted IC_{90} for PI-resistant HIV-1 *in vitro* was no more than 2 μmol/L (specific value not stated).[8]
- *In vitro* work suggests that tipranavir may sustain good inhibitory activity against protease mutants through a unique binding characteristic, whereby it gains, or undergoes a minimal loss in, binding enthalpy in response to mutations.[9] In contrast, in most other agents that maintain activity against mutations, losses in enthalpy (reflecting protease mutations weakening the binding interactions) are compensated for by entropy gains.
- Additive-to-antagonistic antiviral effects were observed *in vitro* when tipranavir was combined with other PIs.[10-14] It was generally additive in combination with NRTIs or NNRTIs[5,14] and synergistic with the fusion inhibitor enfuvurtide.[14]
- Resistance to tipranavir developed slowly *in vitro* and required the sequential development of multiple mutations in the protease gene.[13] Tipranavir-resistant viruses derived from wild-type HIV displayed cross-resistance to other PIs except saquinavir.[13]
- The development of resistance to PIs depends on the number and type of protease gene mutations; broad cross-resistance to traditional, peptidomimetic PIs is associated with substitutions at codons 33, 82, 84 and 90 (key protease mutations).[15] Analysis of clinical isolates from treatment-experienced patients identified the following tipranavir resistance-associated mutations: L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, I84V.[14]
- The effect of baseline HIV phenotype and genotype on response to treatment in comparative phase III trials with tipranavir is discussed in section 2.

Pharmacokinetic Profile

The pharmacokinetics of oral tipranavir alone[16,17] and in combination with riton-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

avir[8,16,18-20] have been evaluated in healthy volunteers[16-19] and HIV-infected patients.[8,19,20]

• Tipranavir is metabolised by cytochrome P450 (CYP) isoenzyme 3A4.[18] It also induces this enzyme.[16] However, when tipranavir is coadministered with ritonavir (a potent CYP3A4 inhibitor) as a boosted regimen, there is net inhibition of the isoenzyme, leading to increased plasma tipranavir concentrations.[16]

• Compared with non-boosted tipranavir, administration of TPV/r 500mg/200mg twice daily in healthy volunteers increased the mean minimum plasma steady-state concentration (C_{minss}) of tipranavir 45-fold (from 0.59 to 26 μmol/L) and mean area under the plasma concentration-time curve (AUC) over the 12-hour dose administration interval (AUC_{12}) 11-fold (from 83 to 934 μmol/L • h), but increased the mean peak concentration only 4-fold (from 30 to 129 μmol/L).[16] The median time to peak concentration for boosted tipranavir was 3 hours.[18] Steady state was reached within 7–10 days (boosted and non-boosted tipranavir).[14,16,18]

• The median C_{minss} values for tipranavir in 72 HIV-infected patients treated with TPV/r 500mg/200mg were 29–32 μmol/L,[8] consistent with the median value in healthy volunteers receiving TPV/r 500mg/200mg (35 μmol/L).[16]

• The absorption of non-boosted tipranavir increases when administered with food (≈2-fold increase in AUC).[17] Based on a population pharmacokinetic analysis of TPV/r 500mg/200mg (n = 187), it appears HIV status, bodyweight and gender may moderately affect tipranavir steady-state concentrations; however, dosage adjustments are not required.[19] Age and race had no, or little, effect on the pharmacokinetics of the drug.[19] Non-boosted tipranavir was highly protein bound (>99%).[16]

• Mild hepatic impairment had no significant effect on systemic exposure to tipranavir following multiple doses of TPV/r 500mg/200mg.[21] There are limited data on the effects of moderate,[21] and no data on severe, hepatic insufficiency and thus tipranavir is contraindicated in patients with moderate to severe hepatic impairment.[14]

• Tipranavir is excreted mainly in faeces (82% of a radioactive dose) with only 4% eliminated in urine.[18] It is eliminated largely as unchanged drug (70–85% in faeces). The median tipranavir elimination half-life for TPV/r 500mg/200mg was 4 hours.[18] Mean tipranavir clearance was 1.0–1.3 L/h for TPV/r 250–1000mg/200mg twice daily (not reported specifically for 500mg dosage).[16]

Pharmacodynamic/Pharmacokinetic Considerations

• The mean[16]/median[8,16] tipranavir C_{minss} achieved with TPV/r 500mg/200mg in healthy volunteers[16] and HIV-infected patients[8] was >20 μmol/L (i.e. >10 times the protein-adjusted 90% inhibitory concentration for PI-resistant virus [section 1.1]). In a clinical study (BI 1182.52; see section 2), a C_{minss} above this concentration was achieved in 79% of patients receiving this dosage.[8]

• Based on data from 329 highly treatment-experienced patients who received TPV/r 500mg/200mg in phase III clinical trials (section 2), a median reduction in plasma HIV RNA levels (viral load) of >1 log_{10} was achieved at week 4 in those with an inhibitory quotient (IQ) ≥45.[20] This was maintained through to week 24 in those with an IQ ≥60, among whom 48% had a viral load of <400 copies/mL at this timepoint. Tipranavir IQ was calculated by dividing the C_{min} by the wild-type protein-adjusted IC_{50}.

Drug Interactions

As well as the interaction with ritonavir, which is used to boost tipranavir bioavailability, tipranavir has the potential to interact with other drugs. The net effect of the combination of tipranavir 500mg with ritonavir 200mg is inhibition of CYP3A and induction of P-glycoprotein (P-gp), while tipranavir itself is a substrate of both CYP3A and P-gp.[14] Thus, there is the potential for interactions between TPV/r and drugs that are substrates of CYP3A and/or P-gp or induce these systems or inhibit P-gp; however, coadministration with other CYP3A inhibitors is

unlikely to affect tipranavir concentrations. Additional details are available in the manufacturer's prescribing information.[14]

- Coadministration of fluconazole[22] or clarithromycin[23] with TPV/r increased the AUC_{12} of tipranavir by 56% and 59% and C_{min} by 104% and 112%. Patients receiving these combinations require careful monitoring. Tipranavir inhibited the formation of the clarithromycin metabolite 14OH-CLR, which is relevant for some pathogens.[23] Coadministration with antacids decreased tipranavir AUC by up to 33%.[17,24]
- Coadministration with TPV/r increased the AUC_{∞} of atorvastatin 9-fold,[24] and that of rifabutin and its main metabolite by 3- and 21-fold.[25] Patients should be monitored, and rifabutin regimens altered to three times weekly or alternate days.[25]
- Although modest pharmacokinetic interactions occur, dosage adjustments are not required when TPV/r is administered with abacavir,[26] didanosine,[26,27] lamivudine,[26] stavudine,[26] tenofovir,[27] zidovudine,[26,27] efavirenz[26,27] or nevirapine.[26] However, enteric-coated didanosine should not be taken within 2 hours of TPV/r.[14]
- Coadministration of TPV/r with other PIs led to decreased exposure to saquinavir, amprenavir and lopinavir among HIV-infected patients in an ongoing clinical trial (BI 1181.51; interim analysis).[28,29] AUC values were reduced by 45–70% (n = 134) and C_{min} values were reduced by 55–81% (n = 173), and these combinations are not recommended.[14]

2. Therapeutic Efficacy

The efficacy of TPV/r 500mg/200mg twice daily has been evaluated in two large, randomised, nonblind, comparative phase III trials in HIV-infected adults with extensive antiretroviral experience.[30,31]

These trials, known as RESIST (Randomized Evaluation of Strategic Intervention in multidrug reSistant patients with Tipranavir)-1[30] and RESIST-2,[31] compared TPV/r with a comparator ritonavir-boosted PI (CPI/r). Data from a planned interim analysis at 24 weeks have been reported for each study.[30,31] Analyses of pooled data from both trials are also available.[32-35]

Based on resistance testing, an appropriate CPI/r (either lopinavir, saquinavir, amprenavir or indinavir, boosted with 100–200mg ritonavir[36]) was pre-selected for each patient before randomisation took place.[30,31] Ritonavir-boosted lopinavir (LPV/r) was specified as the comparator for patients who had not received it previously and had genotypic resistance testing showing sensitivity or possible (as opposed to definite) resistance to LPV/r.[36] Patients who were resistant to all PIs could be enrolled. All patients received an optimised background regimen (which could include enfuvirtide [T20]).[30,31]

RESIST-1 recruited patients from the US, Canada and Australia[30] while RESIST-2 used centres in Europe and Latin America.[31] Patients had received at least three classes of antiretroviral therapy previously (including at least two PI-containing regimens), had one or more primary PI mutations (but no more than two key mutations at codons 33, 82, 84 or 90) and were failing a PI-regimen at the time of entry (viral load ≥1000 copies/mL). There were no CD4+ cell count restrictions.[30,31] Patients in the CPI/r arm who experienced virological failure after week 8 could receive tipranavir in a rollover study.

The primary efficacy variable was treatment response, which was defined as a confirmed ≥1 $\log_{10}$ decrease in plasma HIV RNA levels (viral load) from baseline at 24 weeks. Secondary endpoints included the proportion of patients with undetectable viral load, absolute change in viral load and change in CD4+ cell count. TPV/r was compared with the composite results for the CPI/r arm. Results are reported for intention-to-treat analyses; noncompleters were counted as failures for the primary endpoint and for the proportion of patients with undetectable viral load, while for other endpoints the last observation was carried forward.[30,31]

Additional data come from a randomised, double-blind phase II trial (known as BI 1182.52)[15,37-39] that compared efficacy, safety and plasma concentration data for various TPV/r dosage regimens in order to determine the dosage for use in the phase III trials. It enrolled a similar patient population to the

phase III studies, with the exception that no more than one mutation at codons 82, 84 or 90 was allowed.[37,39]

All data in this section were reported in abstracts and associated posters or presentations.

RESIST-1[30] and RESIST-2[31] randomised and treated 620 and 863 highly treatment-experienced patients (although the 24-week dataset for RESIST-2 included only 539 patients because the analysis was performed when the last patient had reached 16 weeks[31]). Outcomes were similar for the two trials and while individual trial results are presented for the primary endpoint and baseline characteristics, pooled data from both studies are presented for secondary endpoints.

Baseline demographics were similar between groups in both studies. Median baseline plasma HIV RNA level (all patients) was 4.8 $\log_{10}$ copies/mL in each trial;[30,31] median CD4+ cell count was 123 cells/mm^3 in RESIST-1[30] and 185 cells/mm^3 in RESIST-2.[31] The median number of PI mutations was 15 in RESIST-1;[30] this was not reported for RESIST-2 but in pooled data from both trials the median number per group was 16.[34]

The percentage of patients starting on specific ritonavir-boosted comparator PI regimens in RESIST-1[30] and RESIST-2,[31] respectively, were: lopinavir 61% and 38%; saquinavir 21% and 20%; amprenavir 14% and 40%; and indinavir 4% and 3%. Overall for both studies, 86% of patients had virus that was resistant or possibly resistant to the selected PI.[14] Enfuvirtide was part of the background regimen for 36% of patients in RESIST-1[30] and 12% in RESIST-2.[31]

- After 24 weeks' therapy, significantly more patients treated with TPV/r 500mg/200mg than with CPI/r achieved a decrease from baseline in plasma HIV RNA levels of ≥1 $\log_{10}$ copies/mL (treatment response) in both RESIST-1[30] and RESIST-2.[31] Treatment response rates with TPV/r and CPI/r were 42% versus 22% in RESIST-1 and 41% versus 15% in RESIST-2 ($p < 0.0001$ in both trials). The overall response rate from a pooled analysis of both trials is shown in figure 1.[32]

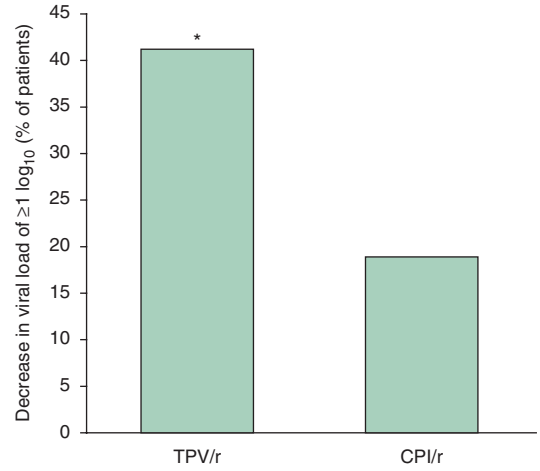

Fig. 1. Efficacy of ritonavir-boosted tipranavir (TPV/r 500mg/200mg) in highly treatment-experienced patients with HIV infection. Data are from a pooled analysis[32] of 24-week data from two randomised, nonblind, multinational trials[30,31] comparing TPV/r (n = 582) with an optimised regimen using currently available ritonavir-boosted protease inhibitors (CPI/r) [n = 577] including lopinavir, saquinavir, amprenavir or indinavir. All patients received optimised background treatment with other antiretroviral drugs; enfuvirtide was received by 27% of TPV/r recipients and 22% of those receiving CPI/r.[32] Treatment response (primary endpoint) was defined as a confirmed decrease in plasma HIV RNA level (viral load) of ≥1 $\log_{10}$ copies/mL from baseline to 24 weeks. * $p < 0.0001$ vs CPI/r.

- In addition, a significantly ($p < 0.001$) higher proportion of patients treated with TPV/r 500mg/200mg achieved undetectable viral loads in both phase III trials.[30,31] A viral load of <400 copies/mL or <50 copies/mL was achieved by 34% and 24% of those treated with TPV/r and by 15% and 9% of CPI/r recipients ($p < 0.0001$ for each comparison; pooled analysis).[32]

- The median total reduction in viral load for the pooled RESIST population was 0.80 $\log_{10}$ copies/mL with TPV/r and 0.25 $\log_{10}$ copies/mL with CPI/r ($p < 0.0001$).[32]

- Numerically more patients in the CPI/r than the TPV/r group had discontinued treatment by 24 weeks because of virological failure in both trials[30,31] (37% vs 6% for pooled data; statistical analysis not reported[32]).

- Based on a pooled analysis,[33] among patients with one to six primary PI mutations at baseline (n = 1151), >40% of patients in the TPV/r group

achieved treatment response at 24 weeks compared with <30% of CPI/r recipients (between group difference significant for those with 1–2 or 3–4 mutations; p = 0.0067 and p < 0.0001). Treatment response was also more frequent with TPV/r than with CPI/r in the presence of 1 or ≥2 (but not 0) key mutations (p = 0.0006 and p < 0.0001).

- A baseline change in IC_{50} of <3-fold (reflecting phenotypic susceptibility) and a low baseline genotypic tipranavir score (the number of mutations known to be associated with tipranavir resistance) were associated with virological response to tipranavir in the RESIST studies.[40] Virological response (defined as ≥0.5 log_{10} decrease in HIV-1 RNA within the first 8 weeks[36]) was achieved in 92% of those with baseline IC_{50} change <3-fold compared with 68% in those with a ≥3-fold change, while tipranavir scores of ≤2, 3–5 and ≥6 were associated with response rates of 94%, 84% and 72%, respectively.
- Pooled RESIST data indicate that treatment response in both TPV/r and CPI/r groups increased progressively with increasing total number of genotypically sensitive antiretroviral drugs used as background therapy (genotypic sensitivity score; GSS), from 13% vs 9% with no background therapy (GSS 0) to 54% vs 36% with three or more such drugs (GSS ≥3) [excluding enfuvurtide which was always considered to be genotypically sensitive; statistical analysis not reported].[34]
- Among TPV/r and CPI/r recipients who received enfuvirtide, treatment response rates were 58% versus 26% compared with 35% versus 17% in those not treated with enfuvirtide.[34] The proportion of patients with undetectable viral load also appeared to be increased among those patients receiving enfuvurtide; for example, a viral load of <50 copies/mL was achieved in 30% vs 13% of recipients of TPV/r or CPI/r plus enfuvurtide compared with overall results (regardless of additional therapy) of 24% vs 9% for the TPV/r and CPI/r groups.[32]
- Efficacy outcomes in patients treated with TPV/r 500mg/200mg at 24 weeks in study BI 1182.52 (n = 72)[37] were similar to those seen in RESIST-1[30] and RESIST-2.[31] In addition, a good antiviral response was seen at 2 weeks in patients with HIV strains with <3 baseline key mutations, an IC_{50} <2-fold that of wild-type virus and an IQ >30,[15,38,39] and the majority of isolates that were resistant to other PIs were susceptible to TPV/r 500mg/200mg.[38,39]
- The median increase in CD4+ cell count was significantly greater with TPV/r than CPI/r in both RESIST-1 (p < 0.001)[30] and RESIST-2 (p = 0.022).[31] In a pooled analysis, it increased by 34 cells/mm^3 (from a baseline of 155 cells/mm^3) with TPV/r compared with 4 cells/mm^3 (baseline 158 cells/mm^3) for the CPI/r group (p < 0.0001).[32]
- There was no significant difference in the number of AIDS progression events over the 24-week analysis period in the phase III trials (3.4% for TPV/r vs 4.6% for CPI/r; pooled data).[32]
- The effect of TPV/r on health-related quality of life (assessed using the 35-item Medical Outcomes Study HIV instrument) was at least as good as that of CPI/r after 24 weeks' treatment in the phase III studies.[35] There was no significant between-group difference in the primary endpoints (mental and physical health summary scores) in RESIST-1 (n = 620), while in RESIST 2 (n = 494) there was a significant difference between groups for change in mental health summary score (3.6; p < 0.05) in favour of TPV/r.

3. Tolerability

Tolerability data are largely derived from the clinical trials discussed in section 2[30-32] and from another study (BI 1181.51) for which short-term safety data (but not the main efficacy analysis) have been reported.[28,29]

- The most common adverse events with TPV/r 500mg/200mg (both overall and for moderate-to-severe events) were gastrointestinal, and included diarrhoea and nausea.[30,31] See figure 2 for the incidence of grade 2–4 events in phase III trials.[32]
- The types of adverse events seen with TPV/r were similar to those seen with CPI/r in RESIST-1[30] and RESIST-2.[31] However, the incidence of events was numerically higher in the TPV/r than the CPI/r group in both trials[30,31] (82% vs 77%

for pooled data[32]). More patients in the TPV/r than in the CPI/r arms discontinued treatment because of adverse events (pooled incidence 8% vs 4%).[30-32]

- TPV/r has been associated with clinical hepatitis and hepatic decompensation, including some episodes resulting in death (incidence not stated).[14] Patients coinfected with chronic hepatitis B or C are at increased risk of hepatotoxicity.[14]
- In the phase III trials,[30,31] grade 3 or 4 elevations of ALT and AST were more common in the TPV/r than the CPI/r groups (6% vs 2% for ALT and 4% vs 1% for AST based on pooled data[32]); differences were statistically significant (all $p < 0.05$) except for AST in RESIST-1. Patients tended to be asymptomatic; ≈1% discontinued treatment because of these elevations.[30,31]
- Grade 3 or 4 abnormalities of lipid levels were also more frequent among recipients of TPV/r than of CPI/r in the phase III studies (3% vs 0.3% for total cholesterol and 21% vs 11% for triglycerides for pooled data[32]).[30,31] Differences were statistically significant (all $p < 0.05$) in both studies.[30,31]
- In an interim analysis of a study evaluating TPV/r 500mg/200mg alone and in combination with other ritonavir-boosted PIs (all twice daily) in 296 highly treatment-experienced patients with high levels of PI resistance,[28,29] the incidence of adverse events was similar for all dual-boosted PI groups (ritonavir-boosted lopinavir/tipranavir, saquinavir/tipranavir and amprenavir/tipranavir) and the TPV/r group at weeks 2–4 (48%, 42%, 54% and 46%, respectively).

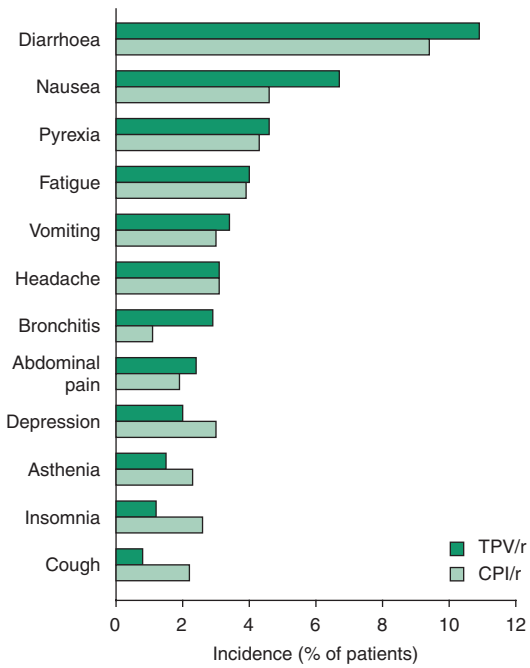

Fig. 2. Moderate to severe (grade 2–4) adverse events with ritonavir-boosted tipranavir (TPV/r) 500mg/200mg. Data are from a pooled analysis[32] of 24-week data from two randomised, nonblind, multinational trials[30,31] comparing TPV/r (n = 746) with an optimised regimen using a standard ritonavir-boosted protease inhibitor (CPI/r) [n = 737] such as lopinavir, saquinavir, amprenavir or indinavir. All patients received optimised background treatment with other antiretroviral drugs.[32]

4. Dosage and Administration

Tipranavir 500mg (two 250mg capsules) is coadministered with ritonavir 200mg twice daily.[14] Tipranavir must be administered with low-dose ritonavir to ensure adequate plasma concentrations of tipranavir are achieved and it should be taken with food to enhance absorption (section 1.2) and tolerability.[36]

It is contraindicated in patients with moderate or severe hepatic insufficiency and in patients receiving certain drugs metabolised primarily by CYP3A. Patients with chronic hepatitis B or C coinfection require close monitoring. Further information, including other warnings, precautions and details of potential drug interactions, are available in the manufacturer's prescribing information.[14]

5. Tipranavir: Current Status

TPV/r has recently been approved by the US FDA for use as part of combination antiretroviral treatment in HIV-1 infected adults with evidence of viral replication who are highly treatment-experienced or who have multiple PI-resistant virus.[41] Two large, well designed phase III trials have demonstrated efficacy for TPV/r 500mg/200mg in this patient population.

References

1. Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in

HIV-1-infected adults and adolescents. 2005 Apr 7 [online]. Available from URL: http://AIDSinfo.nih.gov [Accessed 2005 May 10]

2. Hirsch MS, Brun-Vezinet F, Clotet B, et al. Antiretroviral drug resistance testing in adults infected with human immunodeficiency virus type 1: 2003 recommendations of an International AIDS Society-USA panel. Clin Infect Dis 2003; 37: 113-28
3. Zeldin RK, Petruschke RA. Pharmacological and therapeutic properties of ritonavir-boosted protease inhibitor therapy in HIV-infected patients. J Antimicrob Chemother 2004; 53 (1): 4-9
4. Plosker GL, Figgitt DP. Tipranavir. Drugs 2003; 63 (15): 1611-8
5. Poppe SM, Slade DE, Chong KT, et al. Antiviral activity of the dihydropyrone PNU-140690, a new nonpeptidic human immunodeficiency virus protease inhibitor. Antimicrob Agents Chemother 1997 May; 41 (5): 1058-63
6. Larder BA, Hertogs K, Bloor S, et al. Tipranavir inhibits broadly protease inhibitor-resistant HIV-1 clinical samples. AIDS 2000 Sep 8; 14 (13): 1943-8
7. Rusconi S, La Seta Catamancio S, Citterio P, et al. Susceptibility to PNU-140690 (tipranavir) of human immunodeficiency virus type 1 isolates derived from patients with multidrug resistance to other protease inhibitors. Antimicrob Agents Chemother 2000 May; 44 (5): 1328-32
8. Yeni P, MacGregor T, Gathe J, et al. Correlation of viral load reduction and plasma levels in multiple protease inhibitor (PI)-experienced patients taking tipranavir/ritonavir in a phase IIB trial: BI 1182.52 [abstract no. 528 plus poster]. 10th Conference on Retroviruses and Opportunistic Infections; 2003 Feb 10-14; Boston (MA)
9. Muzammil S, Kang LW, Armstrong AA, et al. Unique response of tipranavir to multi-drug resistant HIV-1 proteases suggests new ways of combating drug resistance [abstract no. 63]. Antiviral Ther 2005; 10 Suppl. 1: S70
10. Chong KT, Pagano PJ. In vitro combination of PNU-140690, a human immunodeficiency virus type 1 protease inhibitor, with ritonavir against ritonavir-sensitive and -resistant clinical isolates. Antimicrob Agents Chemother 1997 Nov; 41 (11): 2367-73
11. Bulgheroni E, Citterio P, Croce F, et al. Analysis of protease inhibitor combinations *in vitro*: activity of lopinavir, amprenavir and tipranavir against HIV type 1 wild-type and drug-resistant isolates. J Antimicrob Chemother 2004 Mar; 53 (3): 464-8
12. Molla A, Mo H, Vasavanonda S, et al. In vitro antiviral interaction of lopinavir with other protease inhibitors. Antimicrob Agents Chemother 2002 Jul; 46 (7): 2249-53
13. Doyon L, Tremblay S, Wardrop E, et al. Characterization of HIV-1 isolates showing decreased susceptibility to tipranavir and their inhibition by tipranavir containing drug mixtures [abstract plus poster]. XII International HIV Drug Resistance Workshop; 2003 Jun 10-14; Los Cabos, Mexico
14. Aptivus® (tipranavir) capsules, 250mg: prescribing information. Ridgefield (CT): Boehringer Ingelheim, 2005 Jun 23
15. McCallister S, Kohlbrenner V, Squires K, et al. Characterization of the impact of genotype, phenotype, and inhibitory quotient on antiviral activity of tipranavir in highly treatment-experienced patients [abstract no. 12]. Antiviral Ther 2003 Jun; 8 (3): S15-6. Plus poster presented at the XII International HIV Drug Resistance Workshop; 2003 Jun 10-14; Los Cabos, Mexico
16. MacGregor TR, Sabo JP, Norris SH, et al. Pharmacokinetic characterization of different dose combinations of coadministered tipranavir and ritonavir in healthy volunteers. HIV Clin Trials 2004 Dec; 5 (6): 371-82
17. Baldwin JR, Borin MT, Wang Y, et al. Effects of food and antacid on bioavailability of the protease inhibitor PNU-140690 in healthy volunteers [abstract no. 649]. 5th Conference on Retroviruses and Opportunistic Infection; 1998 Feb 1-5; Chicago (IL)
18. Valdez H, Sabo J, Wruck J, et al. Tipranavir (TPV) excretion mass balance and metabolite profile when coadministered with ritonavir (r) [abstract no. A-455 plus poster]. 44th ICAAC; 2004 Oct 30-Nov 2; Washington, DC, 17
19. Yong C-L, Sabo J, Oksala C, et al. Population pharmacokinetic assessment of systemic steady-state tipranavir concentrations for adults administered tipranavir/ritonavir 500/200mg twice daily [abstract no. 654 plus poster]. 12th Conference on Retroviruses and Opportunistic Infections; 2005 Feb 22-25, Boston [online]. Available from URL: http://www.retroconference.org [Accessed 2005 Mar 4]
20. Valdez H, McCallister SM, Hall DB. Most highly treatment-experienced recipients of tipranavir/ritonavir (TPV/r) achieve inhibitory quotients (IQ) that are associated with large week 24 viral load (VL) reductions [abstract no. 039 plus presentation]. HIV DART; 2004 Dec 12-16; Montego Bay, Jamaica
21. Cooper C, van Heeswijk R, Bilodeau M, et al. The pharmacokinetics (PK) of single-dose and steady-state Tipranavir/Ritonavir (TPV/r) 500mg/200mg in subjects with mild or moderate hepatic impairment [abstract no. 45 plus poster no. 3.11]. 6th International Workshop on Clinical Pharmacology of HIV Therapy; 2005 Apr 28-30; Quebec City [online]. Available from URL: http://www.hivpresentation.com [Accessed 2005 Jun 16]
22. van Heeswijk R, Sabo JP, MacGregor TR, et al. The effect of tipranavir/ritonavir 500/200 mg bid (TPV/r) on the pharmacokinetics of fluconazole in healthy volunteers [abstract no. 4.8 plus poster]. 5th International Workshop on Clinical Pharmacology of HIV Therapy; 2004 Apr 1-3; Rome
23. van Heeswijk R, Sabo J, MacGregor T, et al. The effect of tipranavir/ritonavir 500/200mg bid (TPV/r) on the pharmacokinetics (PK) of clarithromycin (CLR) in healthy volunteers [abstract no. A-457]. 44th ICAAC 2004 Oct 30-Nov 2; Washington, DC [online]. Available from URL: http://www.abstractsonline.com [Accessed 2005 Mar 3]
24. van Heeswijk R, Sabo JP, Cooper C, et al. The pharmacokinetic interactions between tipranavir/ritornavir 500/200 mg bid (TPV/r) and atorvastatin, antacid, and CYP3A4 in healthy adult volunteers [abstract no 5.2 plus poster]. 5th International Workshop on Clinical Pharmacology of HIV Therapy; 2004 Apr 1-3; Rome
25. van Heeswijk R, Sabo J, MacGregor T, et al. The pharmacokinetic (PK) interaction between single-dose rifabutin (RFB) and steady-state tipranavir/ritonavir 500/200 mg bid (TPV/r) in healthy volunteers [abstract no. A-456]. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2004 Oct 30-Nov 2; Washington, DC [online]. Available from URL: http://www.abstractsonline.com [Accessed 2005 Mar 4]
26. Goebel FD, Sabo JP, MacGregor TR, et al. Pharmacokinetic drug interaction screen of three doses of tipranavir/ritonavir (TPV/r) in HIV-infected patients on stable highly active antiretroviral therapy (HAART) [abstract plus poster]. HIV DART; 2002 Dec 15-19; Naples (FL)

27. Roszko PJ, Curry K, Braxzina B, et al. Standard doses of efavirenz (EFV), zidovudine (ZDV), tenofovir (TDF) and didanoside (ddI) may be given with tipranavir/ritonavir (TPV/r) [abstract no. 865]. Antiviral ther 2003; 8 Suppl. 1: S248. Plus poster presented at the 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment; 2003 Jul 13-16; Paris

28. Leith J, Walmsley S, Katlama C, et al. Pharmacokinetics and safety of tipranavir/ritonavir (TPV/r) alone or in combination with saquinavir (SQV), amprenavir (APV), or lopinavir (LPV): interim analysis of BI1182.51 [abstract]. 5th International Workshop on Clinical Pharmacology of HIV Therapy; 2004 Apr 1-3; Rome [online]. Available from URL: http://www.hivpresentation.com [Accessed 2005 Feb 4]

29. Curry K, Samuels C, Leith J, et al. Pharmacokinetics and safety of tipranavir/ritonavir (TPV/r) alone or in combination with saquinavir (SQV), amprenavir (APV), or lopinavir (LPV): interim analysis of BI1182.51 [presentation]. 5th International Workshop on Clinical Pharmacology of HIV Therapy; 2004 Apr 1-3; Rome [online]. Available from URL: http://www.hivpresentation.com [Accessed 2005 Feb 4]

30. Hicks C. RESIST-1: a phase 3, randomized, controlled, open-label, multicenter trial comparing tipranavir/ritonavir (TPV/r) to an optimized comparator protease inhibitor/r (CPI/r) regimen in antiretroviral (ARV) experienced patients: 24-week data [abstract no. H-1137a plus presentation]. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2004 Oct 31-Nov 2; Washington, DC [online]. Available from URL: http://www.medadvocates.org [Accessed 2005 Feb 17]

31. Cahn P. 24-week data from RESIST-2: phase 3 study of the efficacy and safety of either tipranavir/ritonavir (TPV/r) or an optimized ritonavir (RTV)-boosted standard-of-care (SOC) comparator PI (CPI) in a large randomized multicenter trial in treatment-experienced HIV+ patients [abstract no. PL 14.3 plus presentation]. 7th International Congress on Drug Therapy in HIV Infection; 2004 Nov 14-18; Glasgow [online]. Available from URL: http://www.abstracts2view.com [Accessed 2005 Jan 24]

32. McCallister S, Kohlbrenner VM, Villacian J, et al. Twenty-four week combined analysis of the tipranavir (TPV) RESIST studies of 1483 treatment-experienced patients given either tipranavir/ritonavir (TPV/r) or an optimized standard of care regimen using one of four ritonavir-boosted comparator PIs (CPI/r) [abstract no. 60 plus presentation]. HIV DART; 2004 Dec 12-16; Montego Bay, Jamaica

33. Schapiro J, Cahn P, Trottier B, et al. Effect of baseline genotype on response to tipranavir/ritonavir (TPV/r) compared with standard-of-care comparator (CPI/r) in treatment-experienced patients: the phase 3 RESIST-1 and -2 trials [abstract no. 104 plus presentation]. 12th Conference on Retroviruses and Opportunistic Infections; 2005 Feb 22-25; Boston [online]. Available from URL: http://www.retroconference.org [Accessed 2005 Mar 3]

34. Cooper D, Hicks C, Cahn P, et al. 24-week RESIST study analyses: the efficacy of tipranavir/ritonavir (TPV/r) is superior to lopinavir/ritonavir (LPV/r), and the TPV/r treatment response is enhanced by inclusion of genotypically active antiretrovirals in the optimized background regimen (OBR). [abstract no. 560 plus poster]. 12th Conference on Retroviruses and Opportunistic Infections; 2005 Feb 22-25; Boston [online]. Available from URL: http://www.retroconference.org [Accessed 2005 Mar 4]

35. Wu A, Huang IC, Lobo F, et al. Health-related quality of life with tipranavir in combination with an optimized background regimen in 2 randomized clinical trials [abstract no. 617 plus poster]. 12th Conference on Retroviruses and Opportunistic Infections; 2005 Feb 22-25; Boston [online]. Available from URL: http://www. retroconference.org/2005 [Accessed 2005 Mar 4]

36. Data on file, Phase Five Communications, New York, 2005

37. Kohlbrenner V, Gathe J, Pierone G, et al. Tipranavir/ritonavir (TPV/r) demonstrates potent efficacy in multiple protease inhibitor (PI)-experienced patients at 24 weeks: BI 1182.52 [abstract no. 7.2/2 plus poster]. 9th European AIDS Conference and 1st EACS Resistance and Pharmacology Workshop; 2003 Oct 25-29; Warsaw, 47

38. Squires K, McCallister S, Lazzarin A, et al. Tipranavir/ritonavir (TPV/r) demonstrates a robust resistance profile in multiple protease inhibitor-experienced patients: correlation of baseline genotype and antiviral activity in BI 1182.52 [abstract no. 812]. Antiviral Ther 2003; 8 Suppl. 1: S412. Plus poster presented at the 2nd IAS Conference on HIV Pathogenesis and Treatment; 2003 Jul 13-16; Paris

39. Cooper D, Hall D, Jayaweera D, et al. Baseline phenotypic suceptibility to tipranavir/ritonavir is retained in isolates from patients with multiple protease inhibitor experience (BI 1182.52) [abstract no. 596 plus poster]. 10th Conference on Retroviruses and Opportunistic Infections; 2003 Feb 10-14; Boston (MA)

40. Valdez H, Hall DB, Kohlbrenner VM, et al. Non-response to tipranavir is associated with pre-treatment resistance characterized by tipranavir phenotype or genotypic tipranavir score. Antiviral Ther 2005; 10 Suppl. 1: S29

41. Boehringer Ingelheim Pharmaceuticals Inc. US FDA approves new anti-HIV drug Aptivus for use in combination therapy, 2005 Jun 23 [online]. Available from URL: http://www.us.boehringer-ingelheim.com [Accessed 2005 Jun 29]

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