All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Tipranavir (Aptivus®)
Boehringer Ingelheim Ltd

Advice No: 0707 – August 2007

Recommendation of AWMSG

Tipranavir (Aptivus®) should be recommended for use within NHS Wales for the treatment of human immunodeficiency virus (HIV-1) infection, only for the treatment of highly pre-treated adult patients who have failed multiple protease inhibitors (PI), and where resistance profiling suggests it is appropriate.

Use should be in accordance with the British HIV Association (BHIVA) guidance.

Tipranavir (Aptivus®) is not presently recommended for shared care.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

Date: 15th August 2007

The recommendation of AWMSG is:

- Tipranavir (Aptivus®) should be recommended for use within NHS Wales for the treatment of human immunodeficiency virus (HIV-1) infection, only for the treatment of highly pre-treated adult patients who have failed multiple protease inhibitors (PI), and where resistance profiling suggests it is appropriate.

- Use should be in accordance with the British HIV Association (BHIVA) guidance.

- Tipranavir (Aptivus®) is not presently recommended for shared care.

2.0 PRODUCT DETAILS:

2.1 Licensed indication:
Tipranavir, when 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[1].

2.2 Dosing:
The recommended dose of tipranavir is 500mg, co-administered orally with 200mg ritonavir, twice daily[1].

2.3 Market authorisation date: 25th October 2005[2].

2.4 UK Launch date: November 2005

3.0 DECISION CONTEXT

Despite an initial response to highly active antiretroviral therapy (HAART), some patients may experience viral load rebound for example as a result of serious adverse events to therapy, sub-therapeutic drug plasma concentrations (which may be due to poor adherence to drug therapy or drug interactions) and emergence of anti-viral resistant strains[3,4].

Surveillance data from the Health Protection Agency suggest that among treatment-experienced patients, non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance has remained stable in recent years, whereas nucleoside reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI) resistance has declined[4,5]. The number of individuals infected with triple-class resistant viruses who are difficult to treat has fallen from a peak of around 15% in 1999-2001 to around 8% in 2003-2004[5]. In a European longitudinal observational study, the prevalence of triple-class failure at or after 2002 was 15.5% in treatment-experienced patients and 4.8% in treatment-naïve patients. Following six years of treatment with HAART, 21.4% of treatment-experienced patients and 11.2% of previously treatment-naïve patients had experienced triple class virological failure[6].

According to the British HIV Association (BHIVA) 2006 guidelines the goals of treatment for the majority of treatment-experienced patients are to aim for an undetectable and durable HIV plasma viral load suppression, wherever possible, leading to immunological improvement with lack of clinical progression and improvement in quality of life[4].

Where therapy options are available, switching treatment is more likely to be successful when the viral load is lower and the CD4 cell count is higher. Regimens should include at least two (preferably three) active agents identified through resistance testing and the patients prior drug therapy. For patients with fewer therapeutic options, if their CD4 cell count is maintained, it may be better to keep them on a failing regimen which has minimal side effects, pending the development of new treatments with activity against multi-resistant viruses[4].

Tipranavir (Aptivus®) is a PI licensed in combination with ritonavir and other antiretrovirals in highly pre-treated adults with virus resistant to multiple PIs[1].

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

Pooled data from the two pivotal ongoing Phase III trials, RESIST 1 and 2 indicate greater efficacy of tipranavir (boosted with ritonavir) when compared to a comparator PI plus optimised background therapy in highly treatment-experienced HIV-1 infected adults who would otherwise have limited available treatment options. Overall a significantly higher proportion of patients responded to treatment with tipranavir and remained on treatment for a significantly longer proportion of time. The tipranavir group experienced a significantly greater decrease in viral load and increase in baseline CD4 cell count compared to the comparator group for up to 96 weeks. This response was improved further when treatment was combined with enfuvirtide. As expected, predictors for an effective response included patients having lower baseline viral loads, higher CD4 cell counts, less than three baseline PI mutations and receiving less than four prior PI-based regimens. This has been further studied in a paper by Baxter and colleagues, with the development of a tipranavir mutation score and assessment of the number of available active drugs in the regimen being predictors of virological success. Though the overall safety was comparable between groups in the RESIST trials, raised transaminases and hyperlipidaemia were reported more commonly in those patients receiving tipranavir/ritonavir. A warning has been recently added to the Summary of Product Characteristics for Aptivus® recommending that tipranavir with ritonavir should be used with caution in patients who may be at risk of bleeding (refer to section 6.2 for more details). Tipranavir is a substrate, inducer and inhibitor of cytochrome P450 (CYP450) 3A and a substrate, weak inhibitor and potent inducer of P-glycoprotein (p-gp). Ritonavir inhibits several CYP450 isoenzymes and P-gp. Drug interactions are likely to be occur with tipranavir/ritonavir but do occur with other ritonavir-boosted PI regimens.

4.2 Review of the evidence on cost-effectiveness

The base-case ICER versus the manufacturer's choice of comparator (based on the RESIST trials) of £30,631 per QALY gained is at the upper limit of what is considered to be cost-effective. Moreover, by adopting a lifetime horizon of analysis, the ICER exceeds what is regarded as cost-effective. A shorter (e.g. 15 year) time horizon of analysis may be justified by acknowledging that newer agents will become available in the interim. On balance, therefore, WMP are of the opinion that for patients with a Tipranavir Mutation Score of 0-4, and who achieve a treatment response within 8 weeks of starting TPV/r (defined as 0.5 log drop in viral load), tipranavir may be a cost-effective use of healthcare resource when compared with the chosen alternative.

5.0 LIMITATIONS OF DECISION CONTEXT:

Tipranavir is currently unlicensed in children. Experience is limited in females and non-Caucasians. Results on the safety and efficacy of tipranavir from the RESIST trials are available up to 96 weeks. Follow up data will further assess long-term safety and efficacy.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

6.1 Clinical efficacy:

There are two ongoing randomised, open-label phase III pivotal trials, the Randomised Evaluation of Strategic Intervention in multi-drug reSistant patients with Tipranavir (RESIST) studies. Results from these form the majority of the evidence submitted by the company on the clinical efficacy and safety of tipranavir with ritonavir for treatment-experienced HIV-1 infected adults.

Combined analysis of RESIST 1 (US, Canada and Australia) and 2 (Europe and Latin America) at 48 weeks has been published in a peer-reviewed journal[7]. Pooled analysis is possible as the study design and patient populations were similar. 96 week data is available as a conference poster[8].

In both studies patients were randomised 1:1 to receive either: tipranavir/ritonavir (500mg/200mg twice daily) or a comparator PI plus ritonavir (see appendix one). PI choice was based on prior antiretroviral treatment (ART) and genotypic resistance testing. Approximately half (48.6%) of those patients randomised to a comparator PI plus ritonavir received lopinavir. All patients also received an optimised background regimen, which could contain enfuvirtide, a fusion inhibitor that has shown to be effective particularly when used in combination with other drugs to which the patient is susceptible[4]. Prior use of enfuvirtide was reported in 10% of patients in each group.

The population were predominantly male and Caucasian. Inclusion criteria required that patients had received three months or more prior treatment with all three classes of antiretroviral therapy (NRTI, NNRTI and PI) including two or more PI-based regimens, one being at screening. Patients must have had one or more primary PI-associated mutations (30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V or 90M), to verify accumulated resistance, and less than three mutations at codons 82, 84 or 90 as three or more mutations are associated with reduced tipranavir activity[1]. Mutation at codon 90 has not been shown to reduce susceptibility to tipranavir but does increase resistance to most other PIs[9].

The HIV viral load had to be greater than 1000 copies/ml. The CD4 cell count was not part of the inclusion criteria. Results were stratified according to choice of comparator PI and use of enfuvirtide in the background regimen.

If virological failure or a lack of an initial virological response (see appendix one for definitions) was documented after eight weeks of treatment despite acceptable plasma levels of PI, then patients receiving the comparator PI regimen were able to roll over into a companion study (Study 1182.17) where they could receive tipranavir/ritonavir to construct a new regimen. While those patients receiving tipranavir who failed to respond could remain on-study.

For both RESIST studies surrogate markers were used as the primary efficacy end points. These were the proportion of patients with a treatment response at 48 weeks and time to treatment failure through 48 weeks (see appendix one for definitions). Secondary end points included change from baseline in HIV RNA concentrations in plasma (viral load), proportion of patients with viral load less than 400 copies/ml and 50 copies/ml and changes in CD4 cell count throughout the 48 week study period. Trough concentrations of plasma tipranavir (Cmin) were also measured.

Results:
The 48 week combined analysis was done with data pooled from the two RESIST studies. More patients remained on tipranavir/ritonavir 541/747 (72.5%) than those receiving a comparator PI/ritonavir 230/737 (31.2%). The proportion of treatment responders was significantly greater in the tipranavir/ritonavir group 251/746 (33.6%) compared with the comparator PI/ritonavir group 113/737 (15.3%), p<0.0001.

Median time to treatment failure was significantly longer in the tipranavir/ritonavir group than in the comparator PI/ritonavir group: 113 days (range 0->494) versus 0 days (0-119) respectively, p<0.0001. The comparator was 0 days because more than half of the patients in the comparator/ritonavir group did not achieve a treatment response.

The mean decrease in viral load was significantly greater in the tipranavir group versus the comparator group: -1.14 $\log_{10}$ copies/ml (standard deviation [SD]: 1.30) versus -0.54 $\log_{10}$ copies/ml (SD: 1.02), respectively, p<0.0001.

The proportion of patients with HIV RNA concentrations below 400 copies/ml was 30.4% (227) in the tipranavir group versus 13.8% (102) in the comparator group, p<0.0001 and similarly for copies below 50/ml, 22.8% (170) and 10.2% (75), respectively, p<0.0001.

At week 48 the mean increase from baseline in CD4 cell counts was greater in the tipranavir/ritonavir group than in the comparator PI/ritonavir group: 45 cells/microlitres (SD: 104) versus 21 cells/microlitres (SD: 89), respectively p<0.0001.

Predictors of an effective response to treatment with tipranavir were:
Lower concentration of HIV RNA (viral load) at baseline
Having two or fewer primary PI-associated mutations at baseline
Prior treatment with three or fewer PIs
Having a lower mutation score at baseline (see later in this section)
Attaining higher trough concentrations of tipranavir (>40 micromol/l)
Inclusion of enfuvirtide in background regimen (see points to note)

96 week data[8].
At week 96, 197/746 (26.4%) of the intention to treat group, receiving tipranavir/ritonavir, had a treatment response with only 79/737 (10.7%) in the comparator arm (p<0.0001). The proportion of patients with viral loads below 400 copies/ml was 26.9% (201/726) in the tipranavir/ritonavir group and 10.9% (80/737) in the comparator arm, p<0.0001. Similarly the proportion of patients with a viral load less than 50 copies/ml was 20.4% (152/746) in the tipranavir/ritonavir arm versus 9.1% (67/737) in the comparator arm (p<0.0001). The Kaplain Meier estimates of time to treatment failure through 96 weeks indicated a median time of 115 days for the tipranavir/ritonavir group and 0 days for the comparator group.

- Patients had received a median of 12 ARTs (range 3-20) prior to study entry[7].
- Approximately one-third of patients continued to receive the same PI they were taking when screened at study entry[7].
- Study criteria requested prior treatment with all three types of ART but some patients had not received an NNRTI (common to both treatment groups).
- RESIST 2 included UK residents and overall the population is likely to be representative of patients in Wales who would be eligible for treatment.
- Overall the percentage of co-infected hepatitis B or C patients was limited (around 10%).

- Enfuvirtide inclusion in the background regimen was associated with a greater proportion of treatment responders in both groups. Slightly more patients in the tipranavir group received enfuvirtide (22.7%) versus the comparator group (18.3%). A greater response was maintained through week 96. See also appendix one.
- At week 96, 614/737 (88.3%) of the patients had prematurely discontinued treatment in the comparator/ritonavir am compared with 398/746 in the tipranavir/ritonavir arm. Interestingly 480/614 (78%) of the prematurely discontinued patients in the comparator group withdrew for reasons identified as "other". This was much higher than the tipranavir/ritonavir group in whom 45% withdrew for reason stated as "other". A very low percentage of patients were classified as "lost to follow-up" in both arms. Confirmed virological failure was repored in 44.6% and 18.8% for the comparator and tipranavir arms respectively[8].

Additional information was provided but remains commercial in confidence

Tipranavir Mutation Score
HIV1 genotyping and phenotyping data from phase II and III clinical trials were analysed to determine the association of protease mutations with reduced susceptibility and virologic response to tipranavir. A tipranavir mutation score was developed from these analyses, consisting of a unique string of 16 protease positions and 21 mutations. Regression models for predicting virologic response in phase III trials revealed that at each point the tipranavir score was associated with a 0.16 log $_{10}$ copies/ml lower virologic response to tipranavir at week 24. Virologic success with tipranavir was associated with a lower number of points and greater number of active background drugs[11,12]. See also section 8.0 (Summary of Health Economic Evidence) of the report.

6.2 Safety:
In the RESIST trials, to allow for the difference in numbers of patients completing treatment the adverse event rates were adjusted accordingly and reported as events/100 patient-exposure years. Overall after 48 weeks of treatment the exposure-adjusted adverse event profile was similar for both groups. Though rates of adverse events leading to treatment discontinuation were higher for tipranavir 12.4 versus 10.6/100 patient-exposure years for the comparator group.

Grade III or IV elevations in liver enzymes occurred more frequently in the tipranavir group, leading to treatment discontinuation due to raised alanine transaminases in 13 of 66 patients who had follow up data. Most patients remained asymptomatic and could continue treatment with monitoring. However due to the risk of hepatotoxicity, tipranavir is contra-indicated in patients with moderate or severe (Child-Pugh Class B or C) liver disease. Caution is advised in patients who are co-infected with hepatitis B or C as they are at increased risk of hepatotoxicity, Routine monitoring of liver enzymes is recommended in all patients, refer to Summary of Product Characteristics for further details[1].

Grade 3 or 4 laboratory abnormalities reported more commonly in the tipranavir/ritonavir group than the comparator PI/ritonavir group included raised cholesterol (4.3 versus 0.7 rate per 100 patient-exposure years; $p<0.0001$) and raised triglycerides (30.8 versus 23.1 rate per 100 patient-exposure years; $p<0.0001$). The manufacturers consider that dyslipidaemia would not be uncommon in this patient population given the advanced stage of the patient's disease and prior ART[12]. The clinical significance of these findings is unclear.

Lipodystrophy was also more common with tipranavir/ritonavir. The manufacturers note that as patients in the RESIST trials had previously been exposed to a number of ARTs that may each cause lipodystrophy this may distort these findings. Data from studies in treatment-naïve patients are therefore awaited.

Bleeding was reported more frequently in patients receiving tipranavir/ritonavir than those receiving a comparator PI in the RESIST trials. The relative risk at 24 weeks was 1.98 (95% CI: 1.03-3.80). According to a recent Medicines and Healthcare products Regulatory Agency (MHRA) report, the manufacturers of tipranavir have received 14 reports of intracranial haemorrhage including eight fatalities in 6840 HIV-1 infected patients in clinical trials[13]. The median time to haemorrhage onset following the start of therapy was 525 days[14]. Many of these patients had other risk factors that may have contributed to these events. As no pattern of abnormal haematological or coagulation parameters has been identified no specific routine monitoring is currently required. However caution is recommended in patients at increased risk of bleeding due to trauma, surgery, medical conditions or concomitant medications[1, 13].

Mild to moderate rash has been documented in patients receiving tipranavir, the incidence is higher in females and may occur more frequently in those individuals receiving oral contraceptives or hormone replacement therapies[1,9,15].

Tipranavir is a substrate, inducer and inhibitor of cytochrome P450 CYP3A and a substrate, weak inhibitor and potent inducer of P-glycoprotein (P-gp). Co-administration with ritonavir results in net CYP3A inhibition and P-gp induction. Other cytochromes are also affected by tipranavir resulting in a number of potential drug interactions, which are discussed in detail in the Summary of Product Characteristics[1].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:

The choice of treatment for patients with multiple class resistant HIV infection is complex and will be dependent upon viral-resistance, drug tolerability and prior ART regimens. Some patients will have limited therapeutic options. Further information on approaches for management of these patients is provided in the BHIVA guidelines [3,4]. Currently available boosted PIs include atazanavir, fosamprenavir, indinavir, lopinavir and saquinavir. Darunavir (in combination with ritonavir) is a newly licensed PI for highly treatment-experienced HIV-1 infected adults who have failed more than one regimen containing a PI and will be considered by AWMSG during 2007.

Other options include etravirine (available on compassionate release) and there are ARTs currently in development including integrase inhibitors and CCR5 inhibitors[4,12]. These agents are likely to find a role in triple-class experienced patients as part of an optimised background regimen[4].

7.2 Comparative effectiveness:

The majority of treatment-experienced patients will continue to develop resistant viral mutations, limiting future treatment options. Tipranavir was developed with a novel flexible structure to allow close binding to protease active sites, despite the presence of resistant mutations. Preliminary data from the RESIST studies up to 96 weeks found tipranavir/ritonavir provided better response rates than other (optimised) comparator regimens in adults with treatment experienced HIV-1 infection [7,8].

Efficacy was improved when enfuvirtide was included in the background regimen of the tipranavir arm of the study. Subjects with five or more primary PI mutations in their HIV-1 at baseline, who received tipranavir/ritonavir without enfuvirtide, began to lose antiviral activity between Weeks 4 and 8[1]. Further information is provided in the Summary of Product Characteristics. The main comparator chosen in the RESIST studies was lopinavir/ritonavir; lopinavir has activity against resistant viruses and therefore was a reasonable comparator at the time of the study.

The main disadvantages associated with tipranavir are related to its relative safety profile when compared to other PIs. Though the adverse event profile was similar for both treatment arms in the RESIST studies, treatment discontinuation due to adverse effects was more common in the tipranavir arm. Hepatotoxicity was more frequently reported with tipranavir necessitating routine liver function monitoring and caution in patients co-infected with hepatitis B or C. Due to its complex drug interaction profile; dose alteration of concomitant medication including ARTs may be required. Further information is provided in 6.2 (Safety) of this report.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE:

8.1 Overview of the key economic issue for AWMSG to consider

The key economic issues for AWMSG to consider are:

- whether the additional benefits offered by tipranavir compared to current therapy justify the additional cost, and if so,
- whether the total budgetary impact of supporting the use of tipranavir is acceptable

8.2 Review of published evidence on cost-effectiveness

Standard searches by WMP did not identify any published economic evaluation studies of the use of tipranavir.

8.3 Review of company submission on cost-effectiveness

8.3.1 Summary of the evidence

The manufacturer's submission[12] included a cost-utility analysis that compared tipranavir (pharmacokinetically enhanced with ritonavir) with a 'best alternative' comparator protease inhibitor (also boosted with ritonavir) in highly pre-treated adult patients with HIV-1 infection resistant to multiple protease inhibitors.

The analysis was based on the findings of the phase III trials, RESIST 1 and RESIST 2[7], which were projected to a 15-year time horizon. A Markov model was employed, that incorporated 12 health states, defined by CD4+ cell counts and viral load. The model allowed for patients to switch to a new HAART regimen once treatment has failed. The economic model was conducted in targeted patients with a Tipranavir Mutation Score of 0-4 (a method of resistance testing to identify patients susceptible to tipranavir) and who achieve a treatment response within eight weeks of starting tipranavir/ritonavir (defined as 0.5 log drop in viral load).

Disease progression beyond 48-weeks, and following treatment failure was determined by health state-dependent transition probabilities. These probabilities are derived from an unpublished US cohort database of 1,546 HAART experienced patients[16]. It is unclear how similar the patients included in this dataset were to those in RESIST 1 and 2, and whether the US cohort are representative of patients in Wales.

Of particular concern was that, in the model, the proportion of AIDS-defining events in the tipranavir/ritonavir group at 48 weeks was 25%, compared with 32% in the comparator PI/ritonavir group. These figures are substantially (~5 fold) higher than those reported in RESIST 1 and 2. It is unclear whether or not this discrepancy is due to the incidence of AIDS-defining events obtained from the US cohort study being significantly different from RESIST 1 and 2.

The QALY weights used in the model were based on prior analysis of EQ-5D data from approximately 21,000 HIV patients in all stages of health observed in a pooled sample of clinical trial data where CD4 cell count and viral load were also collected[10]. Adverse drug events were not included explicitly in the model.

The model considered only direct healthcare resources and costs incurred by the NHS in Wales. These included the cost of medicines, staff, laboratory, hospital and community care.

Costs and health outcomes are discounted at the recommended rate of 3.5% and varied in the sensitivity analysis.

8.3.2 Summary of the key findings from the company submission on cost-effectiveness:

In the base case analysis, for patients with a baseline tipranavir mutation score of between 0 and 4 and where patients who do not achieve a 0.5 log drop within eight weeks are switched from tipranavir/ritonavir, the modelled evaluation estimates that treatment with tipranavir/ritonavir is associated with an additional discounted cost of £30,631 per additional QALY gained compared to comparator PI/ritonavir.

Several one-way sensitivity analyses were conducted which indicated that the time horizon, the annual discount rate, various costs and assumptions concerning the valuation of QALY weights did not affect the ICER appreciably. The analyses suggest that the base-case estimate is robust, given the assumptions of the model.

8.4 Review of evidence on budget impact*:*

8.4.1 Summary of the evidence

The manufacturer's submission[12] provided a budget impact analysis from 2007 to 2011. The analysis was based on the projected prevalence and incidence of eligible patients in Wales, calculated from published sources on the prevalence of treated HIV patients in Wales[17]. The proportion likely to be prescribed tipranavir was based on the proportion of patients who would be expected to have failed all three classes of antiretroviral drugs (NRTI, NNRTI and PI) [18]; the eligibility of patients, based on figures from the RESIST trials[7]; and on treatment durability[7].

The manufacturer's submission included an extrapolation of prevalent cases of individuals with diagnosed HIV infection who attend for HIV-related care within the NHS in Wales, based on a 12% annual increase. It was assumed that 6% of patients would be expected to have failed all three classes of antiretroviral drugs (NRTI, NNRTI and PI) [18]. Data from the RESIST trials suggest that 45% of screened patients were ineligible for treatment, of which 78% have a tipranavir mutation score of between 0 and 4[7]. This provides an estimate of the target population of 20 in 2007, rising to 32 in 2011.

The annual incident number of patients eligible for tipranavir (with tipranavir score of 0 to 4) was calculated as 5% of the prevalent cases plus the difference in annual increase in prevalence. The basis of this calculation is not clear.

The manufacturer provides two scenarios; one in which only newly incident eligible cases for tipranavir/ritonavir receive treatment, and an alternative in which all relevant prevalent cases receive treatment. In each scenario, the average length of time on treatment for tipranavir/ritonavir is based on the RESIST trial data of 2.05 years[7]. The comparator PI regimen has an assumed mean on-treatment time of 1.53 years before treatment failure[7].

In the incidence-based model, three patients receive tipranavir/ritonavir in 2007, rising to ten in 2011; whilst no patients receive comparator in 2007/8, two in 2009, rising to ten in 2011.

In the prevalence-based model, 20 patients receive tipranavir/ritonavir in 2007, 22 in 2008, then nine in 2009, rising to ten in 2011. No patients receive comparator PI/ritonavir in 2007/8, 16 in 2009, rising to 21 in 2011.

8.4.2 Summary of the key findings from the company submission on budget impact:

Tipranavir (500mg twice daily) costs £16.33 per patient, per day. This increases to £20.83 with the addition of ritonavir. The annual costs of treatments considered the weighted average use of the various antiretroviral medications based on the RESIST trials. For tipranavir/ritonavir, the annual calculated as £19,622 per patient. The mean annual cost of the comparator was £15,440 per patient. No costs besides drug acquisition costs were considered in the budget impact analysis. No reference was made to the possible influence of darunavir on the budget impact of tipranavir.

The estimated budget impact in Wales, given the assumption that only newly incident eligible patients with tipranavir mutation scores of 0-4 receive tipranavir/ritonavir, is £14,326 in 2007, rising to £42,711 in 2011. Assuming all eligible patients with tipranavir mutation score 0-4 receive tipranavir/ritonavir, the budget impact is £83,021 in 2007, £93,160 in 2008, then reducing to £42,711 by 2011.

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- Management of highly treated HIV-1 infected patients is complex and will be based upon criteria such as prior ART, drug sensitivities, patient tolerance and concomitant disease. Further information on the management of treatment-experienced patients can be found in the BHIVA guidelines[3].
- The BHIVA guidelines recommend that if antiretroviral therapy is started in the context of primary HIV infection, it should normally only be in the setting of a clinical trial[3,4]. Clinical trials of existing and investigational agents are very common in HIV-1; so many newly diagnosed and treatment-experienced patients will be being closely monitored for their treatments and outcomes as a normal part of their care.
- The Health Protection Agency, in collaboration with National Public Health Survey for Wales, conduct an annual survey (SOPHID) of all patients seen for HIV related treatment or care[19].
- As tipranavir is intended for patients who are highly pre-treated and may have few therapeutic options available to them, it will be initiated by specialists and therefore would not be currently deemed suitable for shared care.

9.2 Related advice:
Refer to BHIVA Guidelines 2006.

9.3 Previous AWMSG advice

- Darunavir (Prezista®) – pending appraisal in August 2007
- Emtricitabine (Emtriva®) – pending appraisal in June 2007
- Emtricitabine/tenofovir DF (Truvada®) – pending appraisal in June 2007
- Enfurvirtide (Fuzeon®) – accepted for use (supported with restrictions, May 2004)[20]

9.4 Other points:

- Tipranavir is currently being investigated as a therapeutic option for treatment-naïve patients[12].

9.5 Medical Expert
Medical expert opinion was sought and provided prior to the meeting.

9.6 Patient Interest Group
A patient interest group submission by the Terrence Higgins Trust was provided.

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Appendix 1. Additional Clinical Information

Definitions from RESIST 1 and 2[7]:

Confirmed virological response:
HIV RNA decrease from baseline of 1 $\log_{10}$ copies/ml or greater below baseline without having previous treatment failure. This is defined as either two consecutive viral load measurements less than 1 $\log_{10}$ copies/ml below baseline after having achieved a therapeutic response; or one viral load measurement less than 1 $\log_{10}$ copies/ml below baseline followed by permanent discontinuation of study drug or loss to follow-up after two consecutive viral load measurements of 1 $\log_{10}$ copies/ml or greater below baseline.

Virological failure:
HIV RNA decrease from baseline of less than 1 $\log_{10}$ copies/ml in two consecutive assays more than two weeks apart or a viral load less than 1 $\log_{10}$ copies/ml below baseline followed by permanent discontinuation of study drug or loss to follow up.

Lack of an initial virological response:
A viral load drop of less than 0.5 $\log_{10}$ copies/ml from baseline or failure to achieve a viral load of less than 100,000 copies/ml during the first eight weeks of therapy.

Therapeutic response:
Confirmed viral load reduction of 1 $\log_{10}$ copies/ml or greater in two consecutive measurements, without previous virological failure, discontinuation of study drug, introduction of a new drug, loss to follow-up, or death.

Time to treatment failure:
For those who achieved a virological response:
Earliest time to death, treatment discontinuation, or loss to follow-up, introduction of new ART, first occurrence of virological failure, or one viral load reduction of less than 1 $\log_{10}$ copies/ml below baseline followed by permanent discontinuation of study drug or loss to follow-up.
Time to treatment failure for patients who never achieved a confirmed virological response was defined as day 0.

Table One. Treatment assignment of comparator PI (CPI):

CPI	Number of patients
Lopinavir/ritonavir (400mg/100mg)*	359/737 (48.7%)
Amprenavir/ritonavir (600mg/100mg)*	194/737 (26.3%)
Saquinavir/ritonavir (1000mg/100mg or 800mg/200mg)*	162/737 (22%)
Indinavir/ritonavir (800mg/100mg)*	22/737 (3%)

*Twice daily regimens

Table Two. Summary of efficacy results at week 48 of RESIST combined results by use of enfuvirtide (adapted from paper by Hicks et al)[7].

	Tipranavir/ritonavir	CPI/ritonavir	p
Patients with treatment response (ITT), n (%)			
No enfuvirtide	169 (29.3)	86 (14.3)	<0.0001
Enfuvirtide	82 (48.5)	27 (20.0)	
Patients with <400 copies/ml HIV-RNA in plasma, n (%)			
No enfuvirtide	154 (26.7)	77 (12.8)	<0.0001
Enfuvirtide	73 (43.2)	25 (18.5)	
Patients with <50 copies per ml HIV-RNA in plasma, n (%)			
No enfuvirtide	122 (21.1)	56 (9.3)	0.0093
Enfuvirtide	48 (28.4)	19 (14.1)	
Median time to treatment failure, days			
No enfuvirtide	107 (0 to >494-0)	0 (0 to 112.0)	0.0002*
Enfuvirtide	337 (0 to >475.0)	0 (0 to 232.0)	
Mean (SD) change from baseline in viral load (log_{10} copies per ml RNA in plasma, LOCF)			
No enfuvirtide	-0.98 (1.20)	-0.48 (0.95)	<0.0001†
Enfuvirtide	-1.67 (1.46)	-0.82 (1.25)	
Mean (SD) increase in CD4+ cell count (cells/microlitre)			
No enfuvirtide	32 (97)	18 (90)	<0.0001†
Enfuvirtide	88 (114)	33 (85)	

LOCF=last observation carried forward.
p values refer to comparisons between use of enfuvirtide and no use of enfuvirtide, *Cox proportional. †Analysis of variance. (ANOVA).

Appendix 2. Health Economic Review

Summary of relevant published economic evidence

Standard searches conducted by WMP across multiple databases and information portals have not identified any published economic evaluation studies of the use of tipranavir.

Company submission – economic evidence

1. Description of model

The manufacturer's submission included a cost-utility analysis that compared tipranavir (pharmacokinetically enhanced with ritonavir), tipranavir/ritonavir, with a 'best alternative' comparator protease inhibitor (also boosted with ritonavir), comparator PI/ritonavir, in highly pre-treated adult patients with HIV-1 infection resistant to multiple protease inhibitors[12].

The analysis was based on the findings of the phase III trials, RESIST 1 and RESIST 2[7], which were projected to a 15-year time horizon. A Markov model was employed, that incorporated 12 health states, defined by CD4+ cell counts and viral load. The model also consisted of three stages representing, in each case, a switch to a new HAART regimen once treatment has failed. The economic model was conducted in targeted patients with a low Tipranavir Mutation Score of 0-4 (a method of resistance testing to identify patients susceptible to tipranavir) and who achieve a treatment response within eight weeks of starting tipranavir/ritonavir (defined as 0.5 log drop in viral load). Patient movement from initial stage 1 to stages 2 and 3 is based upon the assumption that all HIV/AIDS patients will eventually fail a specific HAART therapy and are required to switch to new therapy. Disease progression beyond 48-weeks, and in stages 2 and 3, was determined by health state-dependent transition probabilities. These probabilities are derived from an unpublished US cohort database of 1,546 HAART experienced patients[16].

The model incorporates available clinical evidence with a detailed costing and quality of life analysis, and is considered to be appropriate for supporting the decision.

2. Population

The study population comprised a hypothetical cohort of HIV-1 infected patients who had previously failed treatment on three classes of antiretroviral treatment. Patients were further required to have a baseline tipranavir mutation score of between 0 and 4, representing a subgroup of approximately 77% of patients participating in RESIST 1 and 2, and for those receiving tipranavir, treatment with tipranavir/ritonavir is terminated if no response (defined as a 0.5 log drop) is seen at eight weeks.

The unpublished US cohort data, which was used to model disease progression, was based on 1,546 HAART-experienced patients. However, no further details are available, other than a claim that the data were validated against other HIV patient cohort databases. It is unclear how similar the patients included in this dataset were to those in RESIST 1 and 2, and whether they are representative of patients in Wales.

3. Perspective and time horizon

The analysis was conducted from the perspective of the NHS in Wales, with direct costs to the NHS in Wales included in the analysis. It is not clear whether personal

social services costs were also included, as the manufacturer's submission did not refer to these explicitly.

The base-case analysis adopted a 15-year time horizon, whereupon 13.5% of patients receiving tipranavir/ritonavir, and 10.5% of patients receiving comparator PI/ritonavir remained alive. This supports the validity of the time horizon chosen for the analysis.

The choice of time horizon, however, is likely to affect the incremental cost-utility ratio significantly. Sensitivity analyses were conducted at shorter time horizons, of one, five and 10 years. An analysis with a lifetime horizon had not been performed.

4. Comparator

The economic analysis compared tipranavir co-administered with ritonavir (500mg/200mg twice daily) plus an optimised background regimen (tipranavir/ritonavir) with a regimen with the best alternative (investigator-selected) ritonavir-boosted comparator PI (comparator PI/ritonavir), as described in RESIST 1 and 2[7]. The choice of 'best alternative' in RESIST 1 and 2 was based on antiretroviral medication history and genotypic resistance test results. Investigators pre-selected the most appropriate comparator PI/ritonavir regimen from: lopinavir-ritonavir (400mg/100mg), indinavir-ritonavir (800mg/100mg), saquinavir-ritonavir (1000mg/100mg or 800mg/200mg), or amprenavir-ritonavir (600mg/100mg) – all twice a day, and a new optimised background regimen for each patient. The optimised background regimen included enfuvirtide in 23% and 18% of patients randomized to tipranavir/ritonavir, and comparator PI/ritonavir, respectively. Prior use of enfuvirtide was reported in 10% of patients in each group[7].

5. Clinical inputs

5.1 Efficacy

Patients entering the model were distributed across 12 health states according to their baseline CD4 cell count and viral load as reported in the RESIST studies. During the first 48 weeks, the hypothetical cohort of patients in the economic model mirrored those patients with a baseline tipranavir mutation score of between 0 and 4 in RESIST 1 and 2. Treatment with tipranavir/ritonavir is terminated if no response (defined as a 0.5 log drop) is seen after eight weeks. Patients may transit among health states at the end of each 3-month Markov cycle. No half-cycle corrections were made. Patients who dropped out of the trial prior to 48 weeks follow-up are assumed to have failed their first stage regimen and are moved to the next stage of the model.

The economic outcome of the model, however, is independent of the incidence of ADEs, as adjusting the incidence of ADEs for each health state in the model, does not influence the ICER. Nevertheless, this may indicate a difference between the trial and cohort populations that may affect the expected health benefits (and costs) beyond the time horizon of the trials, as beyond 48 weeks, modelled patients transit through the health states at the rate specified by a series of transition matrices calculated from the treatment experienced patient cohort. This rate is the same for both treatment arms, and reflects the average progression rate for HAART-experienced patients in each health state.

Additional information was provided here but remains commercial in confidence.

5.2 Health outcomes

Each health state of the Markov model, defined by CD4 cell count and viral load, was assigned a utility score (QALY weight), such that, for instance, patients in a health state of CD4 cell count >500 /ml and viral load (HIV-1 RNA) <400 copies/ml were assigned a QALY weight of 0.954. The least favourable health state (CD4 cell count <50 /ml and viral load at any level) had a QALY weight of 0.781.

The QALY weights were based on prior analysis of EQ-5D data from approximately 21,000 HIV patients in all stages of health observed in a pooled sample of clinical trial data where CD4 cell count and viral load were also collected[10]. The manufacturers argue that the EQ-5D data included in the model were derived from patients enrolled in clinical trials with a large proportion of patients receiving full dose ritonavir, and which therefore predominantly reflected the side-effect profile common to ritonavir. To reduce the potential bias from quality of life measures, minor adjustments to the utility values were made to reflect ritonavir-specific side effects that were reported in a ritonavir clinical trial[23]. Four adverse events (AEs) – abdominal pain, headache, asthenia, and depression – had a measurable effect on the utility weights across all health states. To avoid assigning utility weights biased by ritonavir-related AEs, a weighted mean utility was calculated for each health state assigning the weight to reflect the percent of observations with the four AEs which were observed in the non-ritonavir treated patients.

The basis for adjusting the QALY weights is not clear given that all patients in RESIST 1 and 2 received ritonavir. Furthermore, the manufacturers did not conduct a separate analysis with the unadjusted EQ-5D QALY weights.

The manufacturers acknowledge that the onset of ADEs results in a substantial decrement in health-related quality of life. The consequence of assigning QALY weights to each health state (as defined), and counting ADEs by proportion of individuals in each state, is that the manufacturer's submission has more than likely underestimated the impact of ADEs on health outcomes. The net effect on accrued QALYs is further complicated by the approximate five-fold increase in the incidence in ADEs in the economic model, compared with RESIST 1 and 2. However, the ICER is independent of the incidence of ADEs, as adjusting the incidence of ADEs for each health state in the model does not influence the cost per QALY gained.

A sensitivity analysis was conducted, which applied a utility decrement of 0.42 (a utility valuation associated with a major ADE) to the base case utility values weighted by the incidence of ADEs from the cohort data.

The manufacturer's submission explored the impact of using an alternative measure of health state utility on the ICER, namely the visual analogue scale (VAS). It further compared MOS-HIV scores (obtained from RESIST 1 and 2), with other studies in which both utility and MOS-HIV scores were obtained concurrently. However, in the opinion of the WMP, both methods are likely to be inferior to the valuation of health state utilities by means of the EQ-5D.

5.3 Adverse events

Adverse drug events were not included explicitly in the model. The adjustments made to the health outcomes were to account for the presence of ritonavir, not tipranavir. It is unclear what the impact of the different profiles and incidence of adverse events, between tipranavir/ritonavir and comparator PI/ritonavir, would be on the ICERs.

6. Healthcare resource utilisation and cost

The model considered only direct healthcare resources and costs incurred by the NHS in Wales. These included the cost of medicines, staff, laboratory, hospital and community care. Also included in the model, (and set at 45% of the direct costs) were "indirect costs". However, these were not described in the manufacturer's submission[12], and had no influence on the ICER.

6.1 Acquisition costs

Drug acquisition costs per day for stage 1 of the model were calculated from published BNF prices[24]. Relative usage of the various medications was as reported in RESIST 1 and 2. For stage 2 and stage 3 of the model, the mean daily cost was assumed to equal the average cost of the comparator therapies.

6.2 Non-HAART costs

For non drug costs, units of healthcare resources were not reported separately from total costs, and it was not possible, therefore, to assess how these costs were calculated.

In order to apply non-drug treatment costs for patients in each of the 12 health states, unpublished data from the four UK HIV treatment centres contributing to the NPMS-HHC database were used. The analysis used resource use data on patients who had failed a HAART regimen in the three latest available years 2000 to 2002. These costs were inflated to 2005/6 costs using the NHS health and social service cost inflator.

6.3 Switching costs

Non-HAART costs were further adjusted to separate out routine costs of patients on maintained HAART treatment and the costs associated with switching treatment. The healthcare costs associated with virological failure include additional consultations and tests[25].

6.4 Cost of adverse effects

The cost of managing adverse events was not included (explicitly) in the economic model.

7. Discounting

Costs and health outcomes are discounted at the recommended rate of 3.5%. In sensitivity analysis discount rates of between 0% and 6% are tested.

8. Results

8.1 Base-case analysis of the cost-effectiveness model

Over a time horizon of 15 years and using a discount rate of 3.5%, the mean cost of treatment for patients in the tipranavir/ritonavir arm was estimated to be £230,976 compared to £209,610 in the comparator PI/ritonavir arm, resulting in an incremental cost of £21,367. Patients receiving tipranavir/ritonavir had increased life expectancy of 0.72 years (6.68 vs. 5.96 in the comparator PI/ritonavir group), and 0.70 additional QALYs (5.64 vs. 4.95 in the comparator PI/ritonavir group).

In the base case analysis, for patients with a baseline tipranavir mutation score of between 0 and 4, and where patients who do not achieve a 0.5 log drop within eight weeks are switched from tipranavir/ritonavir, the modelled evaluation estimates that treatment with tipranavir/ritonavir is associated with an additional discounted cost of £30,631 per additional QALY gained compared to comparator PI/ritonavir.

8.2 Sub-group analysis

The model results show that clinical and economic outcomes vary with levels of resistance to tipranavir (as measured by the tipranavir score) and the inclusion of the assumption associated with stopping treatment with tipranavir/ritonavir if a 0.5 log drop was not seen at eight weeks. Including all RESIST patients, the cost per QALY gained is £34,264. The RESIST subgroup with tipranavir mutation score 0-4 (no stopping rule) was associated with a cost per QALY of £33,208; and by including all RESIST patients, with the 8-week response rule, the ICER was £31,151.

9. Sensitivity analysis

A series of one-way sensitivity analyses were conducted, which supported the robustness of the results. These included the time horizon of analysis; the discount rate; different assumptions around the valuation of health state utility and various costs.

9.1 Time horizon

By reducing the time horizon of analysis to 10 and five years, the ICERs decreased to £27,680 and £19,755 per QALY gained, respectively. At a one-year time horizon of analysis, tipranavir/ritonavir dominated comparator PI/ritonavir (less expensive, more effective). Although no sensitivity analysis was conducted for a lifetime horizon of analysis, it would be expected that the ICER exceeds the base-case value of £30,631 per QALY gained.

9.2 Discount rate

When costs were discounted at 6%, and benefits at 1.5%, the ICER reduced to £23,181 per QALY gained.

9.3 QALY valuation

When the decrements in utility associated with AIDS-defining events are included in the analysis, the cost per QALY gained increases to £31,944. Further sensitivity analyses with alternative valuation methods for health state utility result ICERs ranging from £29,185 to £34,774 per QALY gained.

9.4 Healthcare costs

Various assumptions relating to the cost of enfuvirtide, the cost of follow-on therapy and use of ‘double boosting’ in the comparator arm resulted in ICERs ranging from £21,258 to £31,412 per QALY gained. Altering the non-HAART health state costs, or the cost of switching by +/- 20% had a minimal impact of the cost per QALY gained.

9.5 Probabilistic sensitivity analysis

Although the model allowed for elements of a probabilistic sensitivity analysis, the results were not presented.

Company submission – budget impact analysis

1. Description and critique of company submission

The company submission provided a budget impact analysis from 2007 to 2011. The model compared the anticipated costs of tipranavir compared with comparator PI/ritonavir. Details of the data sources, underlying assumptions, and methods of calculation were provided, and figures were based on Welsh sources as far as possible.

The analysis was based on the projected prevalence and incidence of eligible patients in Wales, which was calculated from published sources on the prevalence of treated HIV patients in Wales[17]. The proportion likely to be prescribed tipranavir was based on the proportion of patients who would be expected to have failed all three classes of antiretroviral drugs (NRTI, NNRTI and PI) [18]; the eligibility of patients, based on figures from the RESIST trials[7]; and on treatment durability[7].

2. Perspective and time horizon

The perspective adopted by the budget impact analysis was that of the NHS Wales. The analysis was conducted over the five years from 2007 to 2011.

3. Data sources

3.1 Prevalent cases

The number of prevalent HIV cases in Wales was obtained from the Survey of Prevalent HIV Infections Diagnosed database held by the Health Protection Agency[17]. Its latest figures, for 2005, indicate that there were 758 individuals with diagnosed HIV infection who attend for HIV-related care within the NHS in Wales. The manufacturer's submission included an extrapolation of prevalent cases, based on a 12% annual increase (as had occurred between 2004 and 2005). The figures suggest 958 prevalent cases in 2007, rising to 1521 in 2011.

Based on figures from the UK CHIC study[18], 38% (3,060 of 7,987 followed-up) would be expected to have experienced treatment with all three classes of antiretroviral drugs (NRTI, NNRTI and PI). Approximately 6% of patients (467 of 7,987) would be expected to have failed all three classes.

In the manufacturer's submission, the estimated prevalence of HIV patients having failed three classes of antiretroviral drugs, ranged from 56 in 2007 to 89 in 2011. Data from the RESIST trials suggest that 45% of screened patients were ineligible for treatment, of which 78% have a tipranavir mutation score of between 0 and 4[7]. This provides an estimate of the target population of 20 in 2007, rising to 32 in 2011.

Using a linear regression of HIV prevalence data (2000 to 2005) [17], however, and extrapolating to 2011 suggests a lower prevalence of HIV patients having failed three classes of antiretroviral drugs, ranging from 54 in 2007 to 75 in 2011, and the prevalent number of patients eligible for tipranavir (with tipranavir score between 0 and 4) increasing from 19 in 2007, to 26 in 2011.

3.2 Incident cases

The annual incident number of patients eligible for tipranavir (with tipranavir score of 0 to 4) was calculated as 5% of the prevalent cases plus the difference in annual increase in prevalence. The basis of this calculation is not clear. The manufacturer's submission estimates three incident cases in 2007, rising to five in 2011.

3.3 Anticipated number of patients treated

The manufacturer provides two scenarios; one in which only newly incident eligible cases for tipranavir/ritonavir receive treatment, and an alternative in which all relevant prevalent cases receive treatment. In each scenario, the average length of time on treatment for tipranavir/ritonavir is based on the RESIST trial data of 2.05 years[7]. The comparator PI regimen has an assumed mean on-treatment time of 1.53 years before treatment failure[7]. Treatment times include the modelled rate of mortality (5.5 per 100 person years) [26] and the dropout rate.

In the incidence-based model, three patients receive tipranavir/ritonavir in 2007, rising to ten in 2011; whilst no patients receive comparator in 2007/8, two in 2009, rising to ten in 2011.

In the prevalence-based model, 20 patients receive tipranavir/ritonavir in 2007, 22 in 2008, then nine in 2009, rising to ten in 2011. No patients receive comparator PI/ritonavir in 2007/8, 16 in 2009, rising to 21 in 2011.

3.4 Rates of adoption

No differential rate of adoption was applied.

3.5 Displaced medicine(s)

In the analysis, comparator PI/ritonavir was considered to be the displaced regimen. However, the manufacturer's submission stated that no direct savings would be made[10].

4. Results

4.1 Base-case

Tipranavir (500mg twice daily) costs £16.33 per patient, per day[24]. This increases to £20.83 with the addition of ritonavir. The annual costs of treatments considered the weighted average use of the various antiretroviral medications based on the RESIST trials. For tipranavir/ritonavir, the annual calculated as £19,622 per patient. The mean annual cost of the comparator was £15,440 per patient. No costs besides drug acquisition costs were considered in the budget impact analysis.

The estimated budget impact in Wales, given the assumption that only newly incident eligible patients with tipranavir scores of 0-4 receive tipranavir/ritonavir, is £14,326 in 2007, rising to £42,711 in 2011. Assuming all eligible patients with tipranavir score 0-4 receive tipranavir/ritonavir, the budget impact is £83,021 in 2007, £93,160 in 2008, then reducing to £42,711 by 2011.

4.2 Sub-group analysis

No sub-group analyses were reported.

5. Sensitivity analysis

Besides the two scenarios presented, no sensitivity analyses of the budget impact model were reported.