AWMSG Secretariat Assessment Report – Advice no. 2110
Tipranavir (Aptivus®▼) for the treatment of HIV-1 infection in highly pre-treated children from 2 to 12 years of age with no other therapeutic options

1.0 PRODUCT DETAILS

Licensed indication	Tipranavir (Aptivus®▼) 100 mg/ml oral solution, co-administered with low dose ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infection in highly pre-treated children from 2 to 12 years of age with virus resistant to multiple protease inhibitors. Tipranavir should only be used as part of an active combination antiretroviral regimen in patients with no other therapeutic options[1]. This indication is based on the results of one phase II study investigating pharmacokinetics, safety and efficacy of tipranavir oral solution in mostly treatment-experienced children aged 2 to 12 years. In deciding to initiate treatment with tipranavir, co-administered with low dose ritonavir, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of tipranavir. Initiation of treatment should take into account the combinations of mutations which may negatively impact the virological response to tipranavir, co-administered with low dose ritonavir[1].
Dosing	The recommended dose for children aged 2 to 12 years is 375 mg/m^2 tipranavir co-administered with 150 mg/m^2 ritonavir, twice daily. The paediatric dose should not exceed 500 mg tipranavir/200 mg ritonavir[1].
Marketing authorisation date	23 June 2009[2].
UK Launch date	7 October 2009[3].

2.0 DECISION CONTEXT

2.1 Background

Since the advent of highly-active antiretroviral therapy (HAART), HIV-infected children in Europe have become healthier and almost all are now surviving into adulthood[4]. The aims of treatment with antiretroviral drugs in children infected with HIV-1 are to achieve and sustain full viral load suppression whilst minimising short- and long-term drug toxicity[4]. To limit the risk of virological treatment failure an objective of therapy is to suppress viral load to < 50 copies/ml[5]. For patients who experience sustained rebound in viral load, or who do not achieve viral load suppression after 24–36 weeks on their current treatment regimen, a change of therapy should be considered. The choice of new therapy should be guided by resistance testing to identify which drugs are active, that is, to which resistance has not yet been acquired. In treatment-experienced patients, a new HIV-1 treatment should include at least two, and

preferably three, active agents. If no or few therapy options exist, maintaining the existing failed regimen may simply allow further resistance mutations to accumulate whilst providing limited clinical benefit to the patient[5].

Tipranavir is a non-peptidic protease inhibitor (PI) developed for treatment-experienced patients infected with HIV-1 with PI-resistant mutations[6]. It was first licensed on 25 October 2005 for combination antiretroviral treatment of HIV-1 infection in highly pre-treated adults with no other therapeutic options[7]. In 2009 the licence was extended to include treatment of paediatric patients: the existing capsule formulation was granted a licence extension for treatment of patients aged 12 to 18 years[8]; a new oral solution formulation was licensed for use only in patients aged 2 to 12 years[6]. Both licence extensions apply to the same restricted population as tipranavir in adults: tipranavir is only for use in patients with no other therapeutic options[1,7].

This assessment concerns use of the oral solution formulation in children aged 2 to 12 years. Use of the capsule formulation in adolescents aged 12 to 18 years is the subject of a separate concurrent All Wales Medicines Strategy Group (AWMSG) assessment (advice no. 2010).

2.2 Comparators

By definition of its licensed indication, which states that tipranavir should only be used as part of an active combination antiretroviral regimen in patients with no other therapeutic options[1], there are no comparators for the use of tipranavir within the scope of this report.

2.3 Guidance and related advice

- Paediatric European Network for Treatment of Aids (PENTA) 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection[4].
- British HIV Association (BHIVA) guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy (2008)[5].
- AWMSG Final Appraisal Report: Tipranavir for treatment of HIV infection in highly pre-treated adult patients with virus resistant to multiple protease inhibitors (August 2007)[9]. Tipranavir is recommended for use within NHS Wales for the treatment of HIV-1 infection only for the treatment of highly pre-treated adult patients who have failed multiple PIs, and where resistance profiling suggests it is appropriate. Use should be in accordance with BHIVA guidance[9].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFICACY

3.1 Efficacy study 1182.14

As part of their limited submission[3], the company have cited efficacy evidence from study 1182.14[10]. This was a phase II, 48-week, open-label, randomised trial in paediatric HIV-1-infected patients (n = 115: 112 treatment-experienced, 3 treatment-naive) treated with tipranavir twice daily at one of two doses: 290 or 375 mg/m^2. Tipranavir was administered in combination with ritonavir as part of an optimised, non-PI antiretroviral background regimen. All patients initially received tipranavir oral solution; those aged 12 years or more who reached a body surface area-adjusted dose equivalent to 500 mg twice daily were eligible to switch to treatment with capsules after four weeks[10]. The primary endpoint of this study was the assessment of safety and tolerability of tipranavir in oral solution formulation[8]. Efficacy and pharmacokinetic

outcomes, including virologic load, CD4 cell count and bioavailability, were assessed as secondary endpoints[8].

A total of 62 patients aged 2–12 years were treated with the oral solution formulation of tipranavir during the study[1]. Available efficacy data for this patient group is summarised in table 1, although it should be noted that studying efficacy was not a stated primary objective of the study[8].

Table 1. Efficacy results in patients aged 2–12 years, stratified by age group[6].

	2 to < 6 years	6 to < 12 years
Total treated	25	37
Median change from baseline* in viral load, log_{10} copies/ml		
Week 24	−2.5	−1.7
Week 48	−2.7	−1.0
Week 100	−2.7	−1.2
Median change from baseline† in CD4+ cell count, cells/mm^3		
Week 24	293	133
Week 48	323	143
Week 100	294	121
Number of patients with ≥ 1 log_{10} viral load reduction (%)		
Week 24	20 (80.0)	18 (48.6)
Week 48	19 (76.0)	14 (37.8)
Week 100	14 (56.0)	13 (35.1)
Number of patients with viral load < 50 copies/ml (%)		
Week 24	10 (40.0)	12 (32.4)
Week 48	13 (52.0)	13 (35.1)
Week 100	12 (48.0)	11 (29.7)
Number of patients with viral load < 400 copies/ml (%)		
Week 24	16 (64.0)	15 (40.5)
Week 48	18 (72.0)	13 (35.1)
Week 100	14 (56.0)	11 (29.7)

*Baseline values 5.0 and 4.6 log_{10} copies/ml for patients aged 2 to < 6 years and 6 to < 12 years respectively. †Baseline values 795 and 398 cells/mm^3 for patients aged 2 to < 6 years and 6 to < 12 years respectively.

Clinical efficacy of tipranavir in highly pre-treated HIV-1-infected adults has been previously demonstrated[11]. Pooled data from the two pivotal adult efficacy studies found that 21.1% and 26.7% of adult patients had viral load less than 50 and 400 copies/ml respectively, rising to 28.4% and 43,2% when tipranavir was administered in combination with enfuvirtide[11]. The equivalent figures for children are detailed in table 1. A similar difference between adults and children exists for median changes in viral load and CD4+ cell count. Tipranavir oral solution in children aged 2 to 12 years therefore appears to be more effective than tipranavir capsules in adults, in terms of viral load reduction and CD4+ cell count at 48 weeks, although it should be noted that no statistical analysis of data from study 1182.14 has been performed. Additionally, in the European Public Assessment Report for the tipranavir licence extension, the

Committee for Medicinal Products for Human Use (CHMP) highlight that in trials of other ritonavir-boosted PIs, a similar pattern is observed, with decreased efficacy in adolescents when compared with children[8].

3.2 Bioavailability studies

Studies 1182.45 and 1182.100 were performed in healthy volunteers to assess the relative bioavailability of tipranavir oral solution compared to the capsule formulation.

Study 1182.45 was an open-label, randomised crossover study comparing bioavailability of the two tipranavir formulations in fasted and fed healthy volunteers (n = 30)[6]. In fasted patients, bioavailability was significantly higher for the oral solution than for the capsule formulation. The oral solution when administered to fed patients also resulted in greater bioavailability than capsules given to fasted patients.

Study 1182.100 was a one-sequence, non-randomised crossover study in healthy volunteers (n = 35)[6]. All patients followed the same treatment sequence of 21 doses of tipranavir capsules followed by eight doses of oral solution. The CHMP were critical of the design of this study: the non-randomised nature of the treatment sequence and the lack of washout period mean differences between the two formulations cannot be reliably interpreted. Even if these limitations are discounted, the study did not demonstrate bioequivalence of the two formulations. As with study 1182.45, higher bioavailability was observed for the oral solution than for the capsule formulation of tipranavir[6].

4.0 SUMMARY OF EVIDENCE ON COMPARATIVE SAFETY

Data on safety in the paediatric population is derived from study 1182.14. This suggests that the safety profile of tipranavir in children is comparable to that observed in adults[8]. However, the CHMP considered the results from this study too limited to draw reliable conclusions on safety of tipranavir, in either formulation, in the paediatric population[8].

The concentration of several excipients in the oral solution of tipranavir exceed acceptable daily intake limits[6]. With respect to two of these—vitamin E polyethylene glycol succinate and polyethylene glycol 400—whilst no known side effects have been reported, on the basis of the currently available evidence it cannot be ruled out that a daily intake higher than recommended limits constitutes a risk to patients[6].

In addition to the safety evidence above, it should be noted that during the initial assessment of tipranavir for use in HIV-1-infected adults, the severe safety profile of tipranavir was identified as a major cause for concern[12]. Safety concerns include increased risk of bleeding and poor hepatic tolerability[1,7]. Therefore, as with adult patients, treatment of paediatric patients with tipranavir should be accompanied by close safety monitoring[8].

5.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- With respect to study 1182.14, which compared 290 and 375 mg/m^2 doses of tipranavir oral solution, the CHMP highlight that no clear conclusions can be drawn on the most effective dose within a good safety margin[6]. Therefore it is unclear on what basis the final recommended dose of 375 mg/m^2 has been determined.
- Bioequivalence of the oral solution and capsule formulations of tipranavir has not been demonstrated. The available evidence in fact suggests that oral solution formulation has greater bioavailability than the capsule formulation. This is of particular concern for continued therapy in patients reaching the age of 12, who may be switched from the oral solution to capsule formulation (as required by the respective licensed indications) and could potentially experience a sudden decrease in tipranavir exposure. The effects of this switch have been studied only in the small subgroup within study 1182.14 who underwent a change in formulation from oral solution to tipranavir capsules[6].
- Tipranavir oral solution is significantly less palatable than the capsule formulation[6]. This could have a negative effect on adherence, particularly in paediatric patients who are likely to be sensitive to poor palatability.
- Although the CHMP are of the opinion that more data is needed to draw reliable conclusions on safety of tipranavir (in either formulation) in paediatric patients, some safety concerns exist specifically for the oral solution, namely the uncertainty surrounding its bioavailability and excipient content. Indeed, the switch from tipranavir oral solution to tipranavir capsules at 12 years of age is recommended partly due to the perceived favourable safety profile of the capsules[3].

6.0 SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

6.1 Cost effectiveness evidence

The abbreviated company submission[3] does not include any evidence on the cost effectiveness of the use of tipranavir in patients aged 2 to 12 years.

6.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost effectiveness of tipranavir in this patient population.

7.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

7.1 Budget impact evidence

7.1.1 Context and Methods

The company estimates there to be 18 patients in Wales with HIV-1 infection aged 2 to 12 years in 2010, rising to 27 patients by 2014. These estimates are reportedly based on linear extrapolation of available data from the Health Protection Agency. The proportion of patients estimated to have experienced treatment with three classes of antiretroviral therapy and the proportion that experienced three-class failure, are derived from multicentre cohort studies conducted in the UK and Ireland[13,14]. The proportion of these patients estimated to be eligible for treatment with tipranavir appears to be assumed from the PI mutation profile of patients enrolled in the 48-week open-label trial of tipranavir in children and adolescents[10], but details are lacking.

On this basis, the company estimates that there will be a maximum of one patient aged 2 to 12 years eligible for tipranavir treatment in each of the next five years. Dosing of tipranavir in this population is based on patient body surface area (BSA)[1].

7.1.2 Results

On the assumption of a maximum of one patient eligible for treatment with tipranavir in each of the next five years, the company estimates the maximum annual cost of tipranavir in this population, inclusive of ritonavir, to be in the range £1,852.62 to £6,616.49, depending on patient BSA[3].

The company also notes that paediatric patients with highly treatment resistant HIV-1 infection are usually referred to a paediatric centre in London for treatment initiation[3].

7.1.3 WMP critique of the company's budget impact estimates

The company has made reasonable efforts to estimate eligible patient numbers. The licensed indication stipulates that tipranavir should only be used as part of an active combination antiretroviral regimen in patients with no other therapeutic options; therefore, other protease inhibitors are unlikely to be displaced to a significant extent by the availability of tipranavir. The range of BSAs considered by the company (0.37 to 1.33 m^2) is extracted directly from the Summary of Product Characteristics (SPC) for tipranavir[1]. It should be noted that tipranavir is not recommended for use in patients aged less than 2 years of age[1] and children aged 2 years and above may have a BSA greater than the lower limit of the range considered by the company. The lower limit of the range of maximum annual costs may, therefore, not be as low in practice as that presented by the company.

7.2 Comparative unit costs

Other protease inhibitors are unlikely to be displaced to a significant extent in the target patient population by the availability of tipranavir. Darunavir (Prezista®▼) is licensed for use in highly pre-treated children (aged 6 years and older) and adolescents[7]. Example annual costs, inclusive of ritonavir and based on the dose ranges presented in the respective SPCs[1,15], are presented in Table 2. Treatment must be tailored to the individual patient.

Table 2. Example annual costs of tipranavir and darunavir.

Drug regimen	Patient characteristics	Annual cost[16]
Tipranavir (Aptivus®▼) 375 mg/m^2 oral solution plus ritonavir oral solution 150 mg/m^2 twice daily	Aged 2 to 12 years; BSA range 0.32 to 1.33 m^2*	£1,852.62 to £6,616.49*
Darunavir (Prezista®▼) tablets plus ritonavir oral solution twice daily	Aged 6 years and over: Body weight 20 to 29 kg: 375 mg/50 mg Body weight 30 kg to 39 kg: 450 mg/60 mg Body weight ≥ 40 kg: 600 mg/100 mg	£3,805.58 £4,580.56 £6,254.80
This table does not imply therapeutic equivalence of the drugs or doses. See the individual SPCs[1,15] and BNF for recommendations. All costs calculated from BNF list prices[16] ** See section 7.1.3 for discussion about the range of BSAs considered and costs*		

8.0 ADDITIONAL INFORMATION

8.1 Shared care arrangements

WMP is of the opinion that tipranavir is not suitable for shared care within NHS Wales. Tipranavir should be prescribed by physicians who are experienced in the treatment of HIV-1 infection[1].

This assessment report is based on evidence from a limited submission by Boehringer Ingelheim limited on 27 August 2010.

This report should be cited as:
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