AWMSG Secretariat Assessment Report – Advice no: 2010
Tipranavir (Aptivus®▼) for the treatment of HIV-1 infection in highly pre-treated adolescents 12 years of age or older with no other therapeutic options

1.0 PRODUCT DETAILS

Licensed indication	Tipranavir (Aptivus®▼), co-administered with low dose ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infection in highly pre-treated adults and adolescents 12 years of age or older 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 two phase III studies, performed in highly pre-treated adult patients (median number of 12 prior antiretroviral agents) with virus resistant to protease inhibitors and of one phase II study investigating pharmacokinetics, safety and efficacy of tipranavir in mostly treatment-experienced adolescent patients aged 12 to 18 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 of tipranavir is 500 mg, co-administered with 200 mg ritonavir, twice daily. Since currently only limited efficacy and safety data are available for adolescents, close monitoring of virologic response and tolerance is particularly warranted in this patient group[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[1]. 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[7]; a new liquid formulation was licensed for use only in patients aged 2 to 12 years[7]. 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[1,8].

This assessment concerns use of the capsule formulation in adolescents aged 12 to 18 years. Use of the liquid formulation in patients aged 2 to 12 years is the subject of a separate concurrent All Wales Medicines Strategy Group (AWMSG) assessment (advice no. 2110).

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 should be 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

As part of their limited submission[3], the company have cited efficacy evidence from study 1182.14[10]. This was a phase II, open-label, randomised, 48 week 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 mg/m^2 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[7]. Efficacy and pharmacokinetic outcomes, including virologic load, CD4 cell count and bioavailability, were assessed as secondary endpoints[7].

A total of 29 patients aged 12–18 switched to capsules during the study[1,10]. Patients were eligible to switch formulation after four weeks, but it is not clear how long each patient was treated with the liquid tipranavir formulation before switching. 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[7].

Table 1. Efficacy results for patients aged 12–18 years and treated with tipranavir capsules[7].

Total treated	29
Median change from baseline* in viral load, log_{10} copies/ml	
Week 24	−1.2
Week 48	−0.8
Week 100	−0.4
Median change from baseline† in CD4+ cell count, cells/mm^3	
Week 24	56
Week 48	39
Week 100	45
Number of patients with ≥ 1 log_{10} viral load reduction (%)	
Week 24	13 (44.8)
Week 48	9 (31.0)
Week 100	7 (24.1)
Number of patients with viral load < 50 copies/ml (%)	
Week 24	8 (27.6)
Week 48	8 (27.6)
Week 100	6 (20.7)
Number of patients with viral load < 400 copies/ml (%)	
Week 24	10 (34.5)
Week 48	9 (31.0)
Week 100	7 (24.1)
*Baseline value 4.6 log_{10} copies/ml. †Baseline value 330 cells/mm^3.	

Clinical efficacy of tipranavir in highly pre-treated HIV-1-infected adults has been previously demonstrated[11]. The results presented here in terms of number of patients responding to treatment are similar, but it should be noted that no statistical analysis of data from study 1182.14 has been performed[7].

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[7]. However, the Committee for Medicinal Products for Human Use considered the results from this study too limited to draw reliable conclusions on safety of tipranavir, in either formulation, in the paediatric population[7].

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[1,8]. Therefore, as with adult patients, treatment of paediatric patients with tipranavir should be accompanied by close safety monitoring[7].

5.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- The efficacy of tipranavir capsules in HIV-1 patients aged 12 to 18 years has been studied only in a small, non-randomised subgroup (n = 29) within study 1182.14. However, the Paediatric HIV Expert Group of European Medicines Agency are of the opinion that efficacy does not need to be separately demonstrated in paediatric populations[13]. Extrapolation of data from the adult population, in which extensive studies of this medicine have been carried out, may therefore be acceptable.
- In patients aged 12 to 18 years treated with tipranavir, only a small virologic impact was observed, and efficacy markedly decreased in this age group when compared with patients less than 12 years of age. However, a similar pattern of efficacy decreasing with age is common to all ritonavir-boosted PIs[7].

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 12 to 18 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 39 patients in Wales with HIV-1 infection aged 12 to 18 years in 2010, and that this will rise to 66 patients by 2015. These estimates are reportedly based 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[14,15]. 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 12 to 18 years eligible for tipranavir treatment in each of the next four years, rising to two patients in 2015.

7.1.2 Results

On the assumption of a maximum of one patient eligible for treatment with tipranavir in each of the next four years, the company estimates the maximum annual cost of tipranavir in this population to be £7,005.39, inclusive of the cost of ritonavir which must be given concomitantly[3]. In 2015, this would potentially double to £14,010.78.

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.

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[16]. Annual costs are presented in table 2 for comparative purposes, assuming that all patients aged 12 years and older would have a body weight of > 40 kg. Treatment must be tailored to the individual patient.

Table 2. Example annual costs of tipranavir and darunavir

Drug	Daily regimen	Annual cost[17]
Tipranavir (Aptivus®▼) soft caspules	Tipranavir 500 mg twice daily plus ritonavir 200 mg twice daily	£7,005.39
Darunavir (Prezista®▼) tablets	Darunavir 600 mg twice daily plus ritonavir 100 mg twice daily (assuming body weight > 40 kg)	£6,254.80
This table does not imply therapeutic equivalence of the drugs or doses. See the individual Summaries of Product Characteristics[1,16] and BNF for recommendations. All costs calculated from BNF list prices[17].		

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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