PUBLIC SUMMARY DOCUMENT

Product: Tipranavir, capsule, 250 mg, Aptivus®

Sponsor: Boehringer Ingelheim Pty Ltd

Date of PBAC Consideration: July 2006

1. Purpose of Application

The application requested a Section 100 (Highly Specialised Drugs) listing for tipranavir, for the treatment, in combination with other antiretroviral agents, of HIV infection in antiretroviral experienced patients who have resistance to, or are unable to tolerate multiple protease inhibitors.

2. Background

Tipranavir had not previously been considered by the PBAC.

3. Registration Status:

The TGA registered Aptivus (tipranavir) on 8 June 2006, co-administered with 200mg of ritonavir, for combination treatment of HIV infection in highly antiretroviral treatment experienced adult patients with evidence of viral replication, who have HIV-1 strains resistant to multiple protease inhibitors.

4. Listing Requested and PBAC's view

Section 100 listing (Highly Specialised Drug)
Private Hospital authority required
Treatment, in combination with other antiretroviral agents and co-administered with 200mg ritonavir twice daily, of HIV infection in antiretroviral experienced adults with:

(a) evidence of HIV replication (viral load greater than 10,000 copies per mL), and/or
(b) CD4 cell counts of less than 500 per cubic millimetre.

Patients must have failed previous treatment with, or have resistance to, 3 different antiretroviral regimens, including regimens with at least 1 non-nucleoside reverse transcriptase inhibitor, 1 nucleoside reverse transcriptase inhibitor, and 2 protease inhibitors.

For PBAC's view, see Recommendation and Reasons.

5. Clinical place for the proposed therapy

Current treatment of HIV infection involves the concomitant administration of at least three antiretroviral medications, and is termed Highly Active Antiretroviral Therapy (HAART). Antiretroviral (ARV) drugs are categorised by the specific site at which HIV replication is inhibited.

Current ARV therapies suppress, but do not eradicate HIV. Therefore treatment focuses on attempting to control HIV replication with chronic suppressive therapy. Tipranavir will be used in antiretroviral treatment experienced patients with accumulating protease inhibitor resistance.

6. Comparator

The submission nominated a ritonavir-boosted aggregate of amprenavir, indinavir, lopinavir and saquinavir as the comparator, which was considered appropriate by the PBAC.

7. Clinical Trials

The submission provided two 48-week randomised open-label trials comparing tipranavir/ritonavir with protease inhibitor/ritonavir in treatment-experienced patients. The trials, with identical protocols, were pooled for analysis. Neither trial was published at the time of the submission.

8. Results of the Trials

There was a statistically significant advantage for tipranavir/ritonavir compared to the comparator PI /ritonavir regimens for both treatment response and time to treatment failure. There was no difference in time to treatment failure between the comparator PIs, although time to treatment failure was statistically significantly greater for patients using enfuvirtide as part of their treatment regimen.

The submission presented a number of sensitivity analyses conducted to assess the impact of the open-label trial design and the methodology used for handling missing data. The analyses using non-completers as censored demonstrated results consistent with the key results (non-completers considered failures).

The submission presented adverse events in terms of the rate of first occurrence per 100 person exposure years, which was calculated as the number of patients with an event per 100 years of exposure by patients who received tipranavir or comparator PI therapy. There were more study drug-related adverse events in tipranavir-treated patients (83.4 per 100 patients exposure years compared to 67.8 per 100 patient exposure years in the comparator PI group).

There was a greater rate of diarrhoea in the comparator PI group (21.1 per 100 patient exposure years) than in the tipranavir group (17.6 per 100 patient exposure years), and a higher rate of headache (3.9 verus 2.2) and hypertriglyceridaemia (3.5 verus 1.3) in the tipranavir group compared to the comparator PI group.

There was a statistically significantly greater risk for the Medically Selected Terms (which were PI-specific class events, ARV medication related events or events warranting evaluation because of preclinical or early clinical experience with tipranavir) hepatic events, hyperlipidaemia and fat redistribution in tipranavir-treated patients compared to those treated with comparator PIs.

9. Clinical Claim

The submission described tipranavir as having significant advantages in effectiveness over an alternative protease inhibitor but having more toxicity.

The PBAC accepted that tipranavir has advantages in effectiveness over an alternative protease inhibitor but has more toxicity. However, in reaching this conclusion the PBAC noted the open label trials are associated with potential bias favouring tipranavir due to the ability of comparator PI patients to switch to a roll-over trial using tipranavir. The meta-analysis report addressed this source of bias, however the possibility of bias favouring tipranavir remained.

10. Economic Analysis

A preliminary economic evaluation was presented. The choice of the cost-effectiveness approach was valid. The evaluation assessed the incremental cost per treatment responder at 48 weeks and the incremental cost per month responding to treatment. The resource variables included in the evaluation were drug costs, including costs of tipranavir, ritonavir, comparator PIs, optimised background regimens and enfuvirtide. The trial-based incremental cost/extra treatment responder at 48 weeks was in the range of $45,000 - $ 75,000.

A modelled economic evaluation was presented. The choice of the cost-utility approach was valid. The model was a modified version of a previously published model for HIV/AIDS (Simpson et al., 2001). The model used a three-stage Markov process, in which patients move from one stage of the model to another as they fail therapy and commence a new ARV regimen. Following the initial 48 week period, the transition probabilities in the model were based on an American cohort of 1,546 ARV treatment-experienced patients. The utility values for each health state used in the model were derived from analysis of EQ-5D data obtained from pooled clinical trial data. The clinical trials were American trials.

Costs included in the model were ARV regimen costs (the cost of a PI, co-administered ritonavir, enfuvirtide and the cost of the optimised background regimen), costs of routine aspects of care (physician visits, laboratory tests), costs of commencing a subsequent regimen and costs of AIDS defining illnesses.

Both the base case modelled incremental discounted cost per extra discounted QALY and the base case incremental discounted cost per extra discounted life year gained were in the range of $45,000 - $ 75,000.

11. Estimated PBS Usage and Financial Implications

The likely number of packs dispensed/year was estimated to be < 10,000 in Year 4, with < 10,000 packs of co-administered ritonavir.

The financial cost/year to the PBS was estimated to be up to < $ 10 million in Year 4 of listing.

12. Recommendation and Reasons

The PBAC noted that listing was sought for use in HIV patients who had failed at least three different antiretroviral regimens.

The PBAC accepted that tipranavir has advantages in effectiveness over an alternative protease inhibitor but has more toxicity. However, in reaching this conclusion the PBAC noted the open label trials are associated with potential bias favouring tipranavir due to the ability of comparator PI patients to switch to a roll-over trial using tipranavir. The meta-analysis report addressed this source of bias, however the possibility of bias favouring tipranavir remained. Also, the comparator arm of the trials was a 'suboptimal control' and patients could alter their optimised background regimen. The impact of the latter was not addressed in the submission. The PBAC accepted the Pre-Subcommittee response that trial issues largely stem from ethical considerations, and acknowledgement that the data provided is less than optimal for decision making.

The PBAC noted that there was a statistically significantly greater risk for hepatic events, hyperlipidaemia and fat redistribution in tipranavir-treated patients compared to those treated with comparator PIs, and that the TGA has recommended that the Product Information for tipranavir include a formal boxed warning.

The PBAC noted the preliminary trial based economic evaluation did not allow for effects and costs associated with increased toxicity, risk of hepatic events, hyperlipidaemia and fat redistribution.

Further, the PBAC noted the lack of modelling of effects (disutility) and costs associated with statistically significant increased occurrence of hepatic events and laboratory abnormalities associated with liver function and expected, although not statistically significant, increase in toxicity.

Other concerns identified by the PBAC with respect to the model included the issues of differences in population, practice and preferences in the translation of evidence from EQ-5D in US trial data to an Australian setting thus increasing the uncertainty of ICER estimates, and the inability to verify the transition probabilities used in the model.

Therefore, the PBAC rejected the submission because of the high and uncertain cost-effectiveness ratio because of concerns with the model, including the lack of modelling of the cost of managing toxicity.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Boehringer Ingelheim is working with the PBAC and Pharmaceutical Benefits Branch to address the concerns of the PBAC, and intends to resubmit to the March 2007 PBAC meeting.