PUBLIC SUMMARY DOCUMENT

Product: Tipranavir, capsule, 250 mg, Aptivus®

Sponsor: Boehringer Ingelheim Pty Limited

Date of PBAC Consideration: March 2007

1. Purpose of Application

The application requested a Section 100 (Highly Specialised Drugs) listing for the treatment, in combination with other antiretroviral agents and co-administered with 200 mg ritonavir twice daily, of HIV infection in antiretroviral experienced patients who 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 two protease inhibitors.

2. Background

Tipranavir was considered for the first time at the July 2006 PBAC meeting. The PBAC noted that listing was sought for use in HIV patients who had failed at least three different antiretroviral regimens.

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.

Please refer to the Public Summary Document from the July 2006 PBAC meeting at:
http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbac-psd-mtjuly06

3. Registration Status

Tipranavir was registered by the TGA on 8 June 2006 for co-administration with 200mg of ritonavir in 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)
Treatment, in combination with other antiretroviral agents, and co-administered with 200 mg 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 two protease inhibitors.

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Tipranavir will be used in the treatment of HIV infection in antiretroviral treatment experienced patients with accumulating protease inhibitor resistance.

6. Comparator

The submission nominated ritonavir-boosted protease inhibitor aggregate, which includes amprenavir, indinavir, lopinavir and saquinavir. This was previously agreed by the PBAC.

7. Clinical Trials

The submission presented new trial data, with Week 96 results of the two randomised, open-label trials for which Week 48 results were presented in the July 2006 submission. The 48 week data was published at the time of the submission (as Hicks et al (1996) Durable efficacy of tipranavir-ritonavir in combination with an optimised background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multi-drug reSistant patients with Tipranavir (RESIST) studies: an analysis of combined data from two randomised open-label trials. The Lancet 368(9534):466-75).

8. Results of Trials

The statistically significant advantage for tipranavir was maintained at week 96 however, the proportion of responders had decreased in both treatment arms from week 48 to week 96.

As at week 48, the time to treatment failure at week 96 was statistically significantly longer in patients treated with tipranavir compared to those treated with comparator protease inhibitor as well as in those who used enfuvirtide compared to those who did not use enfuvirtide.

The re-submission provided the Kaplan Meier estimate of time to treatment failure in only those patients who had a treatment response. The time to treatment failure was statistically significantly longer in the tipranavir responder groups compared to the comparator protease inhibitor responder group.

The re-submission also presented a summary of "FDA requested" sensitivity analyses of treatment response at week 48, designed to demonstrate that despite patients being able to alter their optimised background regimen, this potential source of bias did not impact the overall results of the trials.

The re-submission stated that these analyses support the findings of the key analysis (week 48) and provide evidence that despite patients being able to alter their optimised background regimen, this potential source of bias did not impact the overall results of the trials.

The re-submission provided updated results for the occurrence of AIDS defining events (ADEs) and death at week 96. There were no statistically significant differences between

tipranavir-treated and comparator protease inhibitor-treated patients in the rate of ADEs or deaths at week 96 of the trials.

The re-submission presented updated toxicity data for overall adverse events, medically selected terms and Grade 3 or 4 laboratory abnormalities, but did not provide updated data for hepatic events or the use of lipid lowering agents.

The proportion of patients experiencing adverse events or discontinuing due to adverse events was greater in the tipranavir group compared to the comparator PI group. When adjusted for differences in exposure, the rate of events was greater in the comparator PI group than in the tipranavir group.

There was a statistically significant advantage for tipranavir in the occurrence of systemic or severe infections per unit time of exposure, however the rate per patient was still higher in the tipranavir arm due to longer exposure. There were statistically significantly higher rates of hepatitis and hyperlipidemia in tipranavir-treated patients compared to comparator protease inhibitor-treated patients.

9. Clinical Claim

The re-submission described tipranavir as significantly more effective than an optimal alternative protease inhibitor, but with more toxicity. The PBAC considered tipranavir offered a clinical advantage in the high-risk patient group for whom subsidy was sought.

10. Economic Analysis

The resubmission presented an updated preliminary economic evaluation. The evaluation assessed the incremental cost per treatment responder at 48 weeks and the incremental cost per month responding to treatment. The approach taken in the preliminary economic evaluation was the same as that presented in the July 2006 submission, but included costs associated with the management of toxicity.

The re-submission estimated the trial-based incremental cost/extra treatment responder at 48 weeks to be in the range of $45,000 to $75,000.

The resubmission presented an updated modelled economic evaluation. The updated model differed considerably from the July 2006 model in order to address the concerns of the PBAC with the previous model, including:

- use of week 96 trial data;
- inclusion of costs and effects for toxicity data, which were not included in the July 2006 model;
- use of updated drug costs;
- use of revised utility values;
- increased model duration from the July 2006 model;
- decreased cycle length;
- revised health states.

The resubmission estimated the base case incremental discounted cost/extra discounted QALY and the base case incremental discounted cost per extra discounted life year gained to be in the range of $15,000 - $45,000.

11. Estimated PBS Usage and Financial Implications

The re-submission estimated the likely number of packs dispensed per year to be up to less than 10,000 in Year 4. The re-submission estimated the financial cost/year to the PBS to be less than $10 million in Year 4.

12. Recommendation and Reasons

The PBAC noted that this resubmission included an updated price and a new economic model compared with that provided in the previous submission. The revised 12 health states included in the model and the overall assumed transitions between them were a source of concern as it was not clear whether they allow a clinically valid mapping of HIV and risk of death in the patient population for the proposed restriction. However, the PBAC acknowledged that the 12 health states were consistent with the trial data, although there was concern about the extension of the transitions across these health states for the full duration of the model of 28 years. The incremental cost effectiveness ratios (ICERs) per extra QALY and per extra life year gained were more favourable to tipranavir compared to those of the previous submission.

The PBAC noted that there were no statistically significant differences between tipranavir-treated and comparator protease inhibitor-treated patients in the rate of AIDS-defining events or deaths at week 96 of the trials presented in the submission. However the trials did demonstrate that tipranavir has a benefit in terms of reducing viral load in this high risk group of patients who have failed other protease inhibitor therapy, and that a reduced viral load has been accepted internationally as a strong surrogate end point in this disease. In particular, the PBAC accepted a trial-based assessment of viral load results comparing tipranavir with the lopinavir/ritonavir combination as the most frequently prescribed protease inhibitor and with enfuvirtide as the HIV drug with the closest restriction to that requested for tipranavir.

Overall the PBAC considered, despite concerns over the plausibility of the model, that tipranavir offers a clinical advantage in the high risk salvage patient group for whom subsidy is sought and recommended listing on a cost-effectiveness basis over the comparator.

Recommendation
TIPRANAVIR, capsule, 250 mg

Restriction: Private hospital authority required (Highly Specialised Drug)
Treatment, in combination with other antiretroviral agents, and co-administered with 200 mg 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); 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 which have included:
i) at least 1 non-nucleoside reverse transcriptase inhibitor; and
ii) at least 1 nucleoside reverse transcriptase inhibitor; and
iii) at least 2 protease inhibitors.

Pack size: 120

NOTE:
These prices are based on special supply arrangements – see Pharmaceutical Benefits Pricing Authority relativity sheet for full details.

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 pleased that the PBAC has recommended the approval of tipranavir for use in antiretroviral experienced patients in Australia.