PUBLIC SUMMARY DOCUMENT
Product: Arsenic trioxide, solution for I.V. infusion, 10mg in 10mL, Phenasen®
Sponsor: Phebra Pty Ltd
Date of PBAC Consideration: March 2009

1. Purpose of Application

The submission requested an Authority Required listing for the treatment acute promyelocytic leukaemia (APL) in patients who have either failed to respond to or has relapsed following treatment with standard first-line therapy.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Arsenic trioxide was TGA registered on 13 May 2009 for the induction of remission and consolidation in patients with acute promyelocytic leukaemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterised by the presence of the t(15:17) translocation or PML/RAR-alpha gene expression.

4. Listing Requested and PBAC's View

Authority Required

Treatment of acute promyelocytic leukaemia (characterised by the presence of the t(15:17) translocation or PML/RAR-α fusion gene transcript) where the patient has either failed to respond to or has relapsed following treatment with standard first-line therapy

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Acute promyelocytic leukaemia is a form of acute myeloid leukaemia (AML) and accounts for about 10% of acute AML diagnoses. The disease is usually associated with a specific chromosomal translocation between the long arms of chromosomes 15 and 17, referred to as t(15:17). The resulting fusion protein (PML-RARα) is thought to block myeloid cell differentiation and myeloid cells accumulate at the promyelocytic stage. The standard treatment of APL involves the combined use of anthracycline chemotherapy together with all-trans retinoic acid (ATRA).

The availability of arsenic would provide a PBS-subsidised treatment for patients with APL who have either failed to respond to or have relapsed following treatment with standard first-line therapy.

6. Comparator

The submission nominated ATRA and intensive chemotherapy as the comparator. (ATRA has been approved by the TGA but is not listed on the PBS). The PBAC accepted this as appropriate.

7. Clinical Trials

The submission presented a comparison of eleven open-label, single arm studies. Ten studies involved arsenic and one study involved ATRA in combination with chemotherapy. Only

three of the arsenic studies (Lazo et al 2003, Soignet et al 2001 and Soignet et al 1998) used dose regimens for induction and consolidation therapy that are consistent with those recommended in the product information. Most of the primary analyses were based on these three studies and the study involving ATRA and chemotherapy.

These studies had been published at the time of submission, as follows:

Trial ID/First Author	Protocol title/Publication title	Publication citation
Arsenic		
Shigeno et al, 2005	Arsenic trioxide therapy in relapsed or refractory Japanese patients with acute promyelocytic leukemia: updated outcomes of the phase II study and postremission therapies.	International Journal of Haematology. 2005. 82(3):224-9.
Raffoux et al, 2003	Combined treatment with arsenic trioxide and all-trans-retinoic acid in patients with relapsed acute promyelocytic leukemia.	Journal of Clinical Oncology. 2003. 21(12):2326-34.
Lazo et al, 2003	Use of arsenic trioxide (As_2O_3) in the treatment of patients with acute promyelocytic leukemia: the M. D. Anderson experience.	Cancer. 2003. 97(9):2218-24.
Leoni et al, 2002	Arsenic trioxide therapy for relapsed acute promyelocytic leukemia: a bridge to transplantation.	Haematologica. 2002. 87(5):485-9.
Soignet et al, 2001	United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia.	Journal of Clinical Oncology. 2001. 19(18):3852-60.
Shen et al, 2001	Studies on the clinical efficacy and pharmacokinetics of low-dose arsenic trioxide in the treatment of relapsed acute promyelocytic leukemia: a comparison with conventional dosage.	Leukemia. 2001. 15(5):735-41.
Kwong et al, 2001	Arsenic trioxide- and idarubicin-induced remissions in relapsed acute promyelocytic leukaemia: clinicopathological and molecular features of a pilot study.	American Journal of Hematology. 2001. 66(4):274-9.
Westervelt et al, 2001	Sudden death among patients with acute promyelocytic leukemia treated with arsenic trioxide.	Blood. 2001. 98(2):266-71.
Niu et al, 1999	Studies on treatment of acute promyelocytic leukemia with arsenic trioxide: remission induction, follow-up, and molecular monitoring in 11 newly diagnosed and 47 relapsed acute promyelocytic leukemia patients.	Blood. 1999. 94(10):3315-24.
Soignet et al, 1998	Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide.	New England Journal of Medicine. 1998. 339(19):1341-8.
ATRA + chemotherapy		
Thomas et al, 2000	Treatment of relapsing acute promyelocytic leukemia by all-trans retinoic acid therapy followed by timed sequential chemotherapy and stem cell transplantation. APL Study Group. Acute promyelocytic leukemia.	Leukemia. 2000. 14(6):1006-13.

8. Results of Trials

The efficacy analysis was based on overall survival at two years and the proportion of patients achieving clinical complete remission.

Comparing the pooled results for those studies involving dosage regimens for arsenic consistent with the recommended regimen (including Lazo et al. (2003), Soignet et al. (1998) and Soignet et al. (2001)), with Thomas et al. (2000):

- a higher proportion of patients (70%, 95%CI: 54% to 84%) treated with arsenic achieved relapse-free survival at two years compared to patients treated with ATRA and chemotherapy (46%); and
- a slightly higher proportion (95%) of patients receiving ATRA and chemotherapy achieved clinical complete remission compared to patients receiving arsenic (90%, 95%CI: 79% to 97%).

The main adverse events reported were acute promyelocytic leukaemia differentiation syndrome (APLS) with or without leukocytosis, the prolongation of the QT/QTc interval on ECG and peripheral neuropathy.

For PBAC's comments on these results, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed arsenic as superior in terms of comparative effectiveness (overall survival at two years) and superior in terms of comparative safety over re-treatment with ATRA and chemotherapy.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

A modelled economic evaluation was presented in the form of a cost-effectiveness analysis.

The incremental cost per life-years gained was estimated in the submission to be less than $15,000. From the sensitivity analysis, the submission also presented a "worst case" incremental cost effectiveness ratio which was estimated to be between $45,000 – $75,000 per life years gained.

11. Estimated PBS Usage and Financial Implications

The financial cost per year to the PBS was estimated to be less than $10 million per year in Year 5.

12. Recommendation and Reasons

The PBAC recommended listing of arsenic trioxide on the PBS on the basis of high clinical need and uncertain but acceptable cost-effectiveness compared with all-trans retinoic acid (ATRA) and intensive chemotherapy.

The PBAC noted that arsenic trioxide is a highly toxic drug that must be given following strict protocols in specialised units but that when delivered in such a fashion, its toxicities are clinically acceptable for benefits achieved which include survival gains.

The PBAC agreed, based on the comparison across single-arm studies, that arsenic is superior in terms of comparative effectiveness (i.e overall survival at two years) but that it was uncertain that it was superior in terms of comparative safety over re-treatment with ATRA and chemotherapy as it has a different toxicity profile to ATRA and chemotherapy.

The PBAC agreed that the assumptions and the extrapolation used in the modelled evaluation were highly uncertain, and the results of the economic evaluation should be interpreted with caution. The PBAC also considered that the financial costs may be overestimated as cost offsets, such as patient co-payment, are not included in the estimates. The PBAC noted that the results of the univariate and multivariate sensitivity analyses indicated that the model is most sensitive to drug costs, the proportion of patients surviving at 2 years post therapy and the proportion of patients receiving stem cell transplantation.

The PBAC noted that the submission explored the uncertainties in the financial estimates through sensitivity analysis, and the "worst case" ICER was estimated to be between $45,000 – $75,000 per life years gained. This estimate was considered highly uncertain due to the following assumptions made in the submission, the price of ATRA, the number of consolidation cycles (clinical study included 3 but TGA registration allows 1) and the cost to treat potential side effects.

The PBAC noted that arsenic is being used as first-line therapy in patients enrolled in the ALLG first-line Study and that this could lead to a change in the treatment algorithm. The PBAC therefore recommended that PBS-subsidised arsenic be limited to use in relapsed patients who are arsenic naïve to prevent utilisation in the first-line setting where evidence is yet to be presented.

Recommendation
ARSENIC TRIOXIDE, solution for I.V. infusion, 10 mg in 10 mL

Restriction: Authority Required
Induction and consolidation treatment of relapsed acute promyelocytic leukaemia (characterised by the presence of the t(15:17) translocation or PML/RAR-α fusion gene transcript) in a patient who is arsenic naïve at induction.

Max. Qty: 60
Repeats: 2

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