

**6.03 ARSENIC TRIOXIDE  
injection, 10mg in 10mL  
Phenasen<sup>®</sup>, Phebra.**

**1 Purpose of Application**

- 1.1 Arsenic trioxide (ATO) is currently listed on the PBS as an Authority Required (STREAMLINED) benefit for the treatment of patients with refractory or relapsed acute promyelocytic leukaemia (APL) who have not previously received ATO at induction.
- 1.2 The sponsor sought an extension of the current PBS listing for ATO to permit its use as a first-line treatment of APL. The submission claimed that in Australia ATO+ATRA±chemotherapy was already used first-line to treat APL and so was seeking reimbursement for the use of ATO to treat this indication.

**2 Requested listing**

2.1 The requested listing was:

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Price for Max. Amt	Proprietary Name and Manufacturer
ARSENIC TRIOXIDE 10mg/ml injection, 18mg 10x10mL vials	18mg	120 140	\$ [redacted] \$ [redacted] pub hosp \$ [redacted] priv hosp	PHENASEN <sup>®</sup> Phebra

<b>Treatment phase: Induction and consolidation</b>	
Condition	Acute promyelocytic leukaemia
Restriction	Authority Required (STREAMLINED)

- 2.2 The requested listing did not restrict the use of ATO in patients with relapsed APL to those who had not received arsenic prior (naïve) to induction; this is a requirement of the current PBS listing of ATO. The submission did not provide any evidence to substantiate the effectiveness of these regimens in patients with prior experience of ATO, although the current National Comprehensive Cancer Network (NCCN) guidelines for APL recommend ATO as part of therapy following first relapse, irrespective of prior exposure to ATO.
- 2.3 The maximum amount of 18mg is sufficient for a daily infusion of 0.15mg/kg/day for patients up to 120kg. The submission stated that 120 repeats was sufficient to complete induction and consolidation therapy. However, according to the PI, it appears that patients could receive up to 140 days of ATO treatment (low-intermediate risk patients, up to 60 days induction + 80 days consolidation). The PSCR (p4) requested that the maximum number of repeats be increased to 140.
- 2.4 The ESC noted that the requested PBS listing was broader than the TGA indication:

- The TGA-approved PI states that the patient's APL must be characterised by the presence of the t(15:17) translocation or PML/RAR- $\alpha$  gene expression. The submission stated that the requirement for the t(15:17) translocation or PML/RAR- $\alpha$  gene expression has been omitted from the proposed listing because APL typically presents as a medical emergency and, thus, treatment is commenced immediately upon clinical and cytological diagnosis of APL. This is not an issue for previously untreated patients with high risk APL, in whom ATO commences on day 9 of treatment, and so genetic diagnosis could be confirmed prior to commencement of ATO. In contrast, patients with low-intermediate risk APL commence both ATO and ATRA immediately, based on morphological diagnosis; this is likely to result in inappropriate initiation of ATO treatment in some PML/RAR- $\alpha$  negative patients, although morphological diagnosis of hypergranular (typical) APL has been reported to be highly predictive of underlying PML/RAR- $\alpha$  rearrangements.
  - The dosage recommendations in the TGA-approved PI indicate that, in previously untreated patients with low-intermediate risk APL, ATO should be used in combination with ATRA, while in previously untreated patients with high risk APL, ATO should be administered in combination with ATRA, chemotherapy and prednisolone. The submission correctly noted that ATRA is not available through the PBS.
- 2.5 The ESC noted that the proposed restriction did not contain any criteria regarding the maximum duration of induction therapy, nor did it state that therapy should be discontinued if haematologic complete remission is not obtained by the end of this induction period.
- 2.6 The dosage and administration recommendations in the ATO PI do not provide detailed recommendations regarding the dosage regimen for ATRA when used in combination with ATO, nor does it provide any recommendations regarding the concomitant use of chemotherapy in treatment consolidation.

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

### **3 Background**

- 3.1 TGA status at time of PBAC consideration: ATO was registered on 24 August 2015, for the induction of remission and consolidation in patients with previously untreated APL, in combination with ATRA and/or chemotherapy and whose APL is characterised by the presence of the t(15:17) translocation or PML/RAR- $\alpha$  gene expression.
- 3.2 At the March 2009 PBAC Meeting, ATO was recommended for Authority Required PBS listing for induction and consolidation treatment of relapsed APL (characterised by the presence of the t(15:17) translocation or PML/RAR- $\alpha$  fusion gene transcript) in a patient who has not been previously treated with arsenic at induction.
- 3.3 In patients with relapsed APL, the relapse-free survival at two years following treatment with ATO monotherapy was 70% (95% confidence interval (CI): 54%, 84%), compared to 46% in patients treated with ATRA+chemotherapy. The PBAC recommended listing of ATO for patients with relapsed APL on the basis of high

clinical need and uncertain but acceptable cost-effectiveness compared with ATRA and intensive chemotherapy. The PBAC noted that ATO 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 the benefits achieved, including survival gains.

- 3.4 This is the first submission to the PBAC for ATO+ATRA±chemotherapy for the induction of remission and treatment consolidation in patients with previously untreated APL.

#### **4 Clinical place for the proposed therapy**

- 4.1 APL is a subtype of acute myeloid leukaemia (AML). It occurs in 5-15% of all AML diagnoses. APL usually presents as a medical emergency with a high rate of early mortality, due mainly to haemorrhagic complications. Symptoms include bruising and bleeding (caused by thrombocytopenia or coagulopathy), fever and infection (due to leukopaenia) and fatigue, and dyspnoea (due to anaemia).
- 4.2 In the past, APL was associated with a very high risk of early mortality due to haemorrhage. However, after the introduction of the differentiating agent ATRA, APL became the most curable of all of the AML subtypes.
- 4.3 The submission proposed ATO in combination with ATRA±chemotherapy as an alternative treatment of newly diagnosed APL.

#### **5 Comparator**

- 5.1 The submission nominated ATRA+chemotherapy as the main comparator in previously untreated patients with APL, regardless of risk classification. ATRA is not currently listed on the PBS.
- 5.2 The ESC noted that there are a number of ATRA+chemotherapy induction and consolidation regimens recommended in clinical guidelines and the published literature for the first-line treatment of patients with APL<sup>1</sup>. While the chemotherapy component in all NCCN-recommended regimens is anthracycline-based, there are no definitive data to suggest the superiority of one anthracycline over another, and no clear consensus on the role of other chemotherapeutic agents, such as cytarabine and mitozantrone<sup>2</sup>.
- 5.3 The submission stated that the regimen of ATRA+chemotherapy most recently used in Australia to treat newly-diagnosed patients was the regimen used in the Australasian Leukaemia and Lymphoma Group (ALLG) single-arm study APML3. The APML3 regimen was used as the comparator in the economic model presented

---

<sup>1</sup> References:

National Comprehensive Cancer Network. NCCN Guidelines: Acute Myeloid Leukaemia, Version 1.20152015 17 July 2015 cited 2015; (Version 1.2015). Available from: <http://www.nccn.org>.

Sanz MA, Grimwade D, Tallman MS, Lowenberg B, Fenaux P, Estey EH, et al. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood*. 2009;113(9):1875-91. Epub 2008/09/25

<sup>2</sup> Reference: Coombs CC, Tavakkoli M, Tallman MS. Acute promyelocytic leukemia: where did we start, where are we now, and the future. *Blood Cancer Journal*. 2015;5:e304.

in Section D of the submission. The APML3 study was completed in March 2007, with the last patient recruited in October 2002. Patients in APML3 had either low-intermediate risk or high risk APL and the induction regimen was based on the ATRA+idarubicin (AIDA) 0493 protocol<sup>3</sup>. However, the APML3 regimen was notable for the use of ATRA monotherapy, without concurrent chemotherapy, throughout the consolidation phase. This consolidation regimen is less intensive than the ATRA+chemotherapy regimens recommended in the current NCCN guidelines. Therefore, it was unclear whether the treatment protocol in APML3 was representative of the ATRA+chemotherapy regimens likely to be used in current Australian clinical practice in the absence of ATO, and the economic evaluation in the submission may reflect the cost-effectiveness of ATO relative to an outdated comparator.

- 5.4 While the ESC considered that the submission's nomination of ATRA+chemotherapy as the comparator was appropriate, it noted that the the ATRA+chemotherapy regimens recommended in current clinical guidelines for APL, including the comparator regimen in Lo-Coco 2013 (which was used as key evidence in Section B of the submission), may be more appropriate comparators than the comparator regimen (APML3) used in the submission's economic evaluation.

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

## **6 PBAC consideration of the evidence**

### **Sponsor hearing**

- 6.1 There was no hearing for this item.

### **Consumer comments**

- 6.2 The PBAC noted that no consumer comments were received for this item.

### **Clinical trials**

- 6.3 The submission was based on two head-to-head randomised controlled trials (RCTs) comparing ATO+ATRA±chemotherapy to ATRA+chemotherapy:
- Lo-Coco 2013: a multicentre, open-label randomised, non-inferiority trial, comparing:
    - ATO+ATRA, for both induction and consolidation therapy (with no maintenance therapy), and
    - ATRA+chemotherapy for both induction and consolidation therapy, followed by ATRA+chemotherapy maintenance therapy,in newly diagnosed patients with low-intermediate risk APL; and
  - Shen 2004: a single-centre RCT comparing:
    - ATO+ATRA±chemotherapy induction therapy, chemotherapy consolidation therapy and ATO+ATRA±chemotherapy maintenance therapy, and
    - ATRA±chemotherapy induction therapy, chemotherapy consolidation therapy and ATRA+chemotherapy maintenance therapy, and

---

<sup>3</sup> Reference: Iland H, Bradstock K, Seymour J, Hertzberg M, Grigg A, Taylor K, et al. Results of the APML3 trial incorporating all-trans-retinoic acid and idarubicin in both induction and consolidation as initial therapy for patients with acute promyelocytic leukemia. *Haematologica*. 2012;97(2):227-34. Epub 2011/10/14.

- ATO±chemotherapy for induction, with chemotherapy consolidation therapy and ATO+chemotherapy maintenance therapy, in newly diagnosed patients with both low-intermediate and high risk APL.
- 6.4 The ATO+ATRA regimen used in Lo-Coco 2013 is consistent with the regimen proposed in Section A.3 of the submission for previously untreated patients with low-intermediate risk APL. It was the key evidence presented for this patient subgroup.
- 6.5 Shen 2004 was not presented in the Commentary as the treatment regimens, including the doses of ATRA and ATO, were not consistent with either the regimens proposed in the submission, or with current Australian practice, as acknowledged in the submission.
- 6.6 Two Australian studies were presented as supporting evidence in the submission:
- APML4: a single-arm study assessing ATO+ATRA+chemotherapy induction, ATO+ATRA consolidation therapy, and ATRA+chemotherapy maintenance therapy, in newly diagnosed patients with either low-intermediate and high risk APL; and
  - APML3: a single-arm study assessing ATRA+chemotherapy induction, ATRA monotherapy for consolidation, and ATRA+chemotherapy maintenance therapy, in newly diagnosed patients with either low-intermediate and high risk APL. APML3 was used as a comparator for APML4.
- 6.7 The regimen used in APML4 was not simply the addition of ATO to the APML3 regimen; the use of ATRA and chemotherapy differed between the two regimens in both the induction and consolidation phases.
- 6.8 The ATO+ATRA+chemotherapy regimen used in APML4 is consistent with the regimen proposed in the submission for previously untreated patients with high risk APL. It was the only evidence presented in the submission for this regimen and this patient subgroup. 23 (18.5%) of the patients in APML4 were high risk.
- 6.9 The initial treatment protocol in APML3 did not include maintenance therapy but was amended during the study to include 2 years of maintenance therapy. The submission presents outcomes for the subgroup of patients recruited after the protocol amendment in order to indirectly (unadjusted) compare with APML4. 70/101 (69.3%) of patients in APML3 were recruited subsequent to the protocol amendment introducing maintenance therapy. Of these, 15 (21.4%) were high risk patients.
- 6.10 The ESC acknowledged that two additional publications were presented in the PSCR (p2):
- Iland et al 2015 present a comparison of results for sub-groups of low-intermediate and high risk patients recruited to the APML studies (see Table 2, PSCR p5); and
  - Burnett et al 2015 (Lancet Oncology) has a similar design to the trial reported by Lo-Coco 2013 and includes high risk patients (see Table 3, PSCR p6).
- The results reported in both publications suggest that the relative treatment benefit of adding ATO to the treatment regimen in high risk patients appears to be consistent with that observed in the low-intermediate risk subgroup. These new publications have not been evaluated, but likely have the same limitations as the discussed for the evidence presented in the submission.

6.11 Details of the trials and single-arm studies presented in the submission are provided in the table below.

**Table 1: Trials, single-arm studies and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trial(s)</b>		
Lo-Coco 2013	Lo-Coco F, Avvisati M, Vignetti C, <i>et al.</i> Retinoic acid and arsenic trioxide for acute promyelocytic leukaemia.  Efficace F, Mandelli F, Avvisati G, <i>et al.</i> Randomized phase III trial of retinoic acid and arsenic trioxide versus retinoic acid and chemotherapy in patients with acute promyelocytic leukemia: health-related quality-of-life outcomes.  Protocol APL0406: A randomised phase III study to compare arsenic (ATO) combined to ATRA versus standard ATRA and anthracycline-based chemotherapy (AIDA regimen) for newly diagnosed, non high-risk acute promyelocytic leukemia.	<i>New England Journal of Medicine</i> 2013; 369 (2):111-121.  <i>Journal of Clinical Oncology</i> 2014; 32 (30):3406-3412.  February 2007
Shen 2004	Shen ZX, Shi ZZ, Fang J <i>et al.</i> All-trans retinoic acid/As <sub>2</sub> O <sub>3</sub> combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia.	<i>Proceedings of the National Academy of Science USA</i> 2004; 101 (15): 5328-5335.
<b>Supplementary studies</b>		
APML4	APML4 Clinical Study Report: A phase II trial in patients with previously untreated acute promyelocytic leukaemia to evaluate the effects of: (i) adding arsenic trioxide to all-trans retinoic acid and idarubicin for remission induction; and (ii) adding arsenic trioxide to all-trans retinoic acid as consolidation.  Iland H.J, Bradstock K, Supple S.G, <i>et al.</i> Australasian Leukaemia and Lymphoma Group. All-trans retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4).	July 2014  <i>Blood</i> 2012; 120 (8):1570-1580.
APML3	APML3 Statistical report. A phase II trial in patients with acute promyelocytic leukaemia to evaluate the effects of: all-trans retinoic acid combined with intensive idarubicin during induction and consolidation. Subsequent intermittent all-trans retinoic acid. Molecular monitoring for evidence of incipient relapse.  Iland H, Bradstock K, Seymour J, <i>et al.</i> Australasian Leukaemia and Lymphoma Group. Results of the APML3 trial incorporating all-trans retinoic acid and idarubicin in both induction and consolidation as initial therapy for patients with acute promyelocytic leukemia.	July 2007  <i>Haematologica</i> 2012; 97 (2):227-234.

Source: Table B.2.3, p61 of the submission.

- 6.12 The key features of the relevant direct randomised trial and single-arm studies are summarised in the table below.

**Table 2: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>ATO+ATRA vs. ATRA+chemotherapy</b>						
Lo-Coco 2013	156*	R, OL, MC 34.4 months (range 0.5-55.8 months)	Low	Newly diagnosed low-intermediate risk APL	Event-free survival rate at 2 years from diagnosis OS at 2 years	Not used
<b>ATO+ATRA±chemotherapy (APML4) vs. ATRA+chemotherapy (APML3)</b>						
APML4	124**	Single-arm 4.2 years (range 1 month to 7.3 years)	High	Newly diagnosed low-intermediate and high risk APL	Event-free survival and OS	Used
APML3	70***	Single-arm 4.6 years	High	Newly diagnosed low-intermediate and high risk APL	Event-free survival and OS	Used

MC=multi-centre; OL=open label; R=randomised; OS=overall survival; APL = acute promyelocytic leukaemia.

\* The submission stated that only 150 patients were included in the "ITT" analysis of the primary outcome, as 6 patients could not be evaluated at 24 months, either due to missing data or insufficient follow-up. Therefore, in the Commentary, it is referred to as the modified ITT analysis (mITT)

\*\* Treatment regimens in APML4 are only consistent with those proposed for high risk APL. 23/124 (18.5%) were high risk patients. The results of this relevant subgroup were not presented.

\*\*\* Patients who received maintenance therapy after a protocol amendment (70/101, 69%). Only 15/70 (21.4%) were high risk patients. The results of this relevant subgroup were not presented.

Source: compiled during the evaluation.

- 6.13 The ESC noted that, for low-intermediate risk patients, the overall risk of bias in Lo-Coco 2013 was low. For high risk patients, there was no direct evidence available. The submission relied on an unadjusted indirect comparison of two single-arm studies so it was not certain whether the two populations were exchangeable. The ESC considered that the relevance of the comparison was limited as:
- The results of the comparison between the high risk subgroup in APML4 (n=23) with the subgroup of high risk patients who received maintenance therapy in APML3 (n=15) were not presented;
  - APML3 was unlikely to represent current clinical practice in Australia in the absence of ATO:
    - the treatment protocol was not consistent with clinical practice guidelines that recommend more intensive ATRA+chemotherapy regimens as best practice, especially in high risk patients (see Section A.4), and
    - it was probable that there have been improvements in supportive care, including haemostatic support, since APML3 was conducted (the last patient was recruited in October 2002) (see Section B.4).

- 6.14 Overall, results of the comparison of APML4 and APML3 had a high risk of bias and confounding, with limited applicability to current Australian clinical practice.

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

## Comparative effectiveness

### Low-intermediate risk APL

6.15 The results of Lo-Coco 2013 are summarised below.

**Table 3: Main results from Lo-Coco 2013 for patients with low-intermediate risk APL**

	ATO+ATRA n/N (%) N=77	ATRA+Chemo n/N (%) N=79	Absolute difference (95% CI)	Relative risk (95%CI)
<b>Effectiveness of induction therapy</b>				
HCR after induction	77/77 (100%)	75/79 (94.9%)	5.1% (0.2%, 9.9%)	1.05 (1.00, 1.11)
<b>Event-free survival rate at 2 year*</b>				
mITT <sup>a</sup>	72/74 (97.3%)	65/76 (85.5%)	11.8% (3.0%, 20.5%)	1.14 (1.03, 1.26)
PP	64/66 (97.0%)	61/72 (84.7%)	12.2% (3.0%, 21.5%)	1.14 (1.03, 1.27)
<b>Sensitivity analyses</b>				
i) negative outcome	72/77 (93.5%)	65/79 (82.3%)	11.2% (1.2%, 21.3%)	1.14 (1.01, 1.28)
ii) positive outcome	75/77 (97.4%)	68/79 (86.1%)	11.3% (2.9%, 19.7%)	1.13 (1.03, 1.25)
iii) negative ATO+ATRA positive ATRA+chemo	72/77 (93.5%)	68/79 (86.1%)	7.4% (-2.0%, 16.8%)	1.09 (0.98, 1.21)
Event-free survival over entire follow-up (ITT) <sup>b</sup>	71/77 (92.2%)	64/79 (81.0%)	11.2% (0.7%, 21.7%)	1.14 (1.00, 1.29)
<b>Secondary outcomes</b>				
Overall survival rate at 2 years	76/77 (98.7%)	72/79 (91.1%)	7.6% (0.8%, 14.3%)	1.08 (1.01, 1.17)
Relapse rate				
At 2 years	1/77 (1.3%)	4/79 (5.1%)		
Over entire follow-up <sup>b</sup>	2/77 (2.6%)	5/79 (6.3%)		

ATO = arsenic trioxide; ATRA = all-trans retinoic acid; CI = confidence interval; HCR = haematologic complete remission; mITT = modified intention-to-treat; PP = per protocol

Haematologic complete remission was defined as <5% blasts in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells, no blasts with Auer rods or persistence of extramedullary disease (see Table B.5.2).

<sup>a</sup> mITT: all patients with results available at 2 years, comparing groups according to assigned treatment

<sup>b</sup> Median follow-up 34.4 months (range 0.5-55.8 months). Two patients relapsed later than 2 years after diagnosis.

Sensitivity analyses were performed during the evaluation, as described in Lo-Coco 2013: i) assuming a poor outcome in patients with missing data; ii) assuming a favourable outcome for all patients with missing data; iii) assuming a poor outcome for patients in the ATO+ATRA group and a favourable outcome for patients in the ATRA+chemotherapy group.

Figures in italics were calculated during the evaluation.

\* The log-rank test for the difference in event-free survival curves indicated the superiority of ATO+ATRA over ATRA+chemotherapy (p=0.02)

Source: Lo-Coco 2013

6.16 The results of both the modified intention-to-treat (mITT) and the per protocol (PP) analyses indicated that ATO+ATRA was statistically superior to ATRA+chemotherapy in terms of the event-free survival rate at 2 years after diagnosis in previously untreated patients with low-intermediate APL, when administered in accordance with the regimens used in Lo-Coco 2013. Given that the pre-specified non-inferiority margin was an absolute difference of 5%, the estimated treatment effect (12%) was also likely to be clinically important.

High risk APL

6.17 The results of the single-arm studies APML4 and APML3 are presented below.

**Table 4: Main results from the single-arm studies APML4 and APML3**

	APML4		APML3
	ATO+ATRA+chemotherapy		ATRA+chemotherapy
	ITT n/N (%) [95%CI]	High-risk subgroup n/N (%) [95%CI]	Maintenance subgroup n/N (%) [95%CI]
Proportion of high risk patients	23/124 (18.5%)		15/70 (21.4%)
HCR after induction	112/124 (90.3%) [83.7%, 94.9%]	NR	64/70 (91.4%) [82.3%, 96.8%]
Event-free survival rate at 2 years			
Original definition <sup>a</sup>	109/124 (87.9%) [80.8%, 93.1%]	18/23 (78.3%) [56.3%, 92.5%]	52/70 (74.3%) [62.4%, 84.0%]
Alternative definition <sup>b</sup>	114/124 (91.9%) [85.7%, 96.1%]	19/23 (82.6%) [61.2%, 95.0%]	55/70 (78.6%) [67.1%, 87.5%]
Overall survival rate at 2 years	117/124 (94.4%) [88.7%, 97.7%]	20/23 (87.0%) [66.4%, 97.2%]	63/70 (90.0%) [80.5%, 95.9%]

ATO = arsenic trioxide; ATRA = all-trans retinoic acid; CI = confidence interval; HCR = haematologic complete remission; ITT = intention-to-treat; NR = not reported

<sup>a</sup> Patients with unacceptable toxicity during induction or who withdrew consent during induction were counted as treatment failures.

<sup>b</sup> Patients with unacceptable toxicity during induction or who withdrew consent during induction were not considered treatment failures provided a subsequent response assessment documented HCR. This applied to 9 patients, 4 of whom subsequently had an event, and 5 who were censored at the end of induction treatment, and not counted as treatment failures.

Haematologic complete remission was defined as absence of symptoms and signs of leukaemia, neutrophil count  $\geq 1.0 \times 10^9/L$  and absence of abnormal cells in the peripheral blood differential, platelet count  $\geq 100 \times 10^9/L$ , disappearance from bone marrow of abnormal cells and return of active normal haemopoiesis (see Table B.5.2).

Note: In APML4 the median follow-up time at closeout date was 4.2 years (range 1 month to 7.3 years) p7 APML4 CSR; in APML3, the estimated median potential follow-up using the reverse Kaplan-Meier method was 4.6 years (p229, Iland et al 2012)

Binomial exact 95% CIs were calculated during the evaluation (in STATA)

Source: Table B.6.1, p79. Figure B.6.3 and Table B.6.3, p82 of the submission, Table 20 p43, Table 21 p44, Table 22 p46, Table 24 p46, Table 23 p47, Table 25 p50, Table 28 p63, Figure 32 p65, and Figure 33 p65 APML4 Statistical report

6.18 The submission presented a comparison of the results for the intention-to treat (ITT) population of APML4 (both low-intermediate and high risk) with those for the subgroup of patients in APML3 who received maintenance therapy. Given the unadjusted indirect nature of the comparison, the considerable risk of confounding and bias, and the overlap in the exact binomial 95% confidence intervals, it was not possible to draw any conclusions regarding the comparative effectiveness of the ATO+ATRA+chemotherapy regimen (proposed in the submission for high risk APL) and ATRA+chemotherapy (including maintenance therapy, as used in APML3) in patients with APL. As noted above, the PSCR (p2) provided some evidence to suggest that the relative treatment benefit in high-risk patients may be consistent with that observed in low-intermediate risk patients:

**Table 5: Key results of the AML17 trial (reported by Burnett et al, in press)**

Outcome	ATRA + idarubicin N=119	ATO + ATRA N=116	OR/HR (95% CI)	p-value
Complete remission	106 (89%)	109 (94%)	OR: 0.54 (0.21 – 1.34)	0.18
Confirmed molecular	105 (88%)	106 (91%)	OR: 0.71 (0.31 – 1.65)	0.43

Outcome	ATRA + idarubicin N=119	ATO + ATRA N=116	OR/HR (95% CI)	p-value
negativity				
4-year event-free survival	70% (56% – 80%)	91% (84% - 95%)	HR: 0.35 (0.18 – 0.68)	0.002
- High risk patients	64% (42% - 79%)	87% (68% - 95%)	HR: 0.34 (0.11 – 1.08)	0.07
- Low-intermediate risk patients	71% (55% - 83%)	92% (84% - 97%)	HR: 0.34 (0.15 – 0.75)	0.008
4-year overall survival	89% (81% - 93%)	93% (86%-96%)	HR: 0.60 (0.26 – 1.42)	0.25
- High risk patients	84% (63% - 95%)	87% (68% - 95%)	NR	NR
- Low-intermediate risk patients	90% (81% - 95%)	95% (86% - 98%)	NR	NR

Source: Table 3, PSCR p6

## Comparative harms

6.19 The key safety data from Lo-Coco 2013 and APML4 are summarised below.

**Table 6: Summary of key adverse events in Lo-Coco 2013 and APML4**

Trial ID	Lo-Coco 2013 (low-intermediate risk APL)		APML4 (low-intermediate risk and high risk APL)
	ATO+ATRA n/N (%)	ATRA+chemo n/N (%)	ATO+ATRA+chemo n/N (%)
<b>Deaths</b>			
Induction	0	4/79 (5.1%)	4/124 (3.2%)
Consolidation	1/77 (1.3%)	3/79 (3.8%)	0
Total*	1/77 (1.3%)*	7/79 (8.9%)*	4/124 (3.2%)
<b>Haematologic AEs</b>			
APL DS in induction	15/77 (19.5%)	13/79 (16.5%)	24% <sup>d</sup>
Severe APL DS	5/77 (6.5%)	5/79 (6.3%)	14% (grade 3-4)
Death	0	2/79 (2.5%) <sup>h</sup>	0
Leukocytosis <sup>a</sup> during induction	35/74 (47.3%)	19/79 (2.4%)	13/121 (11%) <sup>e</sup>
Thrombocytopenia Grade 3-4 <sup>b</sup>	Lasting >15 days	Lasting >15 days	
Induction	59%	88%	121/121 (100%) <sup>f</sup>
Consolidation cycle 1	6%	18%	0
Consolidation cycle 2	6%	65%	0
Consolidation cycle 3	3%	15%	
Neutropenia Grade 3-4 <sup>b</sup>	Lasting >15 days	Lasting >15 days	
Induction	46%	79%	121/121 (100%) <sup>f</sup>
Consolidation cycle 1	6%	35%	69/112 (62%) <sup>f</sup>
Consolidation cycle 2	6%	76%	30/112 (27%) <sup>f</sup>
Consolidation cycle 3	4%	25%	
Fever of unknown origin and documented infectious episodes	26 episodes	59 episodes	(N not reported)
Induction			91 (76%)
Consolidation cycle 1			21 (19%)
Consolidation cycle 2			3 (3%)
<b>Non-haematologic AEs</b>			
Hepatotoxicity Grade 3-4	43/68 (63.2%)	4/69 (5.8%)	(N not reported)
Induction			53 (44%)
Consolidation cycle 1			13 (12%)
Consolidation cycle 2			2 (2%)

Trial ID	Lo-Coco 2013 (low-intermediate risk APL)		APML4 (low-intermediate risk and high risk APL)
	ATO+ATRA n/N (%)	ATRA+chemo n/N (%)	ATO+ATRA+chemo n/N (%)
Prolongation of QTc interval	12/77 (15.6%)	0	(N not reported)
Induction			17 (14%)
Consolidation cycle 1			10 (9%)
Consolidation cycle 2			4 (4%)
Gastrointestinal toxicity Grade 3-4	3 (4.4%) <sup>g</sup>	7 (9.9%) <sup>g</sup>	(N not reported)
Induction			33 (28%)
Consolidation cycle 1			3 (3%)
Consolidation cycle 2			1 (1%)
Oral toxicity Grade 3-4	0	14 (19.4%) <sup>g</sup>	NR
Neurological	NR	NR	(N not reported)
Induction			7 (6%)
Consolidation cycle 1			2 (2%)
Consolidation cycle 2			0

AE = adverse event; APL DS = acute promyelocytic leukaemia differentiation syndrome; ATO = arsenic trioxide; ATRA = all-trans retinoic acid; NA = not applicable; NR = not reported

<sup>a</sup> Leucocytosis defined as WCC > 10x10<sup>9</sup>/L

<sup>b</sup> Platelets < 50x10<sup>9</sup>/L; Neutrophil count < 1x10<sup>9</sup>/L,

<sup>c</sup> One patient discontinued due to seizures but subsequently died and is included as a death, rather than a discontinuation.

Source Table 14.1.1, p 105 APML4 CSR

<sup>d</sup> Source: p96 APML4 CSR

<sup>e</sup> Source: Table 14.3.1.3, p155 APML4 CSR

<sup>f</sup> p90 APML4 CSR, Table 29, p99 and Table 14.3.1.1 p144 APML4 CSR.

<sup>g</sup> As reported in Table S3, p12 of Lo-Coco 2013 Supplementary appendix

<sup>h</sup> Two of the 5 patients with severe APL DS.

\* Risk difference -7.6% (95%CI: -14.3%, -0.8%)

Table constructed during the evaluation.

Source for Lo-Coco 2013: Table B.7.1, p 90 of the submission; pp 117-118 and Figure 4 p118 Lo-Coco 2013; Table S3 Lo-Coco 2013 supplementary appendix. Source for APML4: Table B.7.1, p90 of the submission and Table 3, p1575 Iland et al (2012), unless otherwise noted.

- 6.20 The ESC acknowledged that further safety data were provided in Burnett 2015, noting in particular the increase in cardiac toxicity associated with ATO treatment. These additional data were not stratified by risk status.

### Low-intermediate risk APL

- 6.21 In Lo-Coco 2013, ATO replaced the use of chemotherapy in both the induction and consolidation phases. In addition, in contrast to the ATRA+chemotherapy arm, patients in the ATO+ATRA treatment group did not receive maintenance therapy. The difference between the two treatment arms, in terms safety outcomes, reflected the difference in the safety profiles of ATO and chemotherapy.
- 6.22 ATRA+chemotherapy was associated with a higher incidence of grade 3-4 prolonged cytopenias (lasting >15 days), mucositis and infections compared to ATO+ATRA. Only two patients in the ATRA+chemotherapy arm were reported to have discontinued due to prolonged myelosuppression (in the maintenance phase).
- 6.23 Prolongation of QTc interval, leukocytosis, and grade 3-4 hepatic toxicity all occurred more frequently in the ATO+ATRA treatment group compared to the ATRA+chemotherapy group. The hepatic toxic effects were all managed with

temporary discontinuation of study medication, and the leucocytosis was successfully managed with hydroxyurea; neither of these AEs resulted in permanent discontinuation of study drug. Permanent discontinuation of ATO was only required in one of the 12 patients with documented prolongation of the QTc interval.

- 6.24 Given the relatively small sample size and the difference in the toxicity profiles of the regimens, it was not possible to draw any definite conclusions regarding the short-term safety of ATO+ATRA compared to ATRA+chemotherapy. However, the lower mortality observed with ATO+ATRA compared to ATRA+chemotherapy, possibly due in part to reduced neutropenia and thrombocytopenia, and the ability to successfully manage most of the severe AEs associated with ATO, suggested that ATO+ATRA was at least as safe as ATRA+chemotherapy, in the short term, in adult patients with low-intermediate risk APL.

#### High risk APL

- 6.25 In contrast to the ATO+ATRA regimen for low-intermediate risk APL, in APML4 ATO was added to ATRA+chemotherapy in the induction phase, and patients received maintenance therapy. As in Lo-Coco 2013, ATO replaced the use of chemotherapy in the consolidation phase of currently recommended ATRA+chemotherapy regimens. Safety data specific to patients with high risk APL were not provided.
- 6.26 The submission stated that higher rates of AEs were reported during the induction phase for ATO+ATRA+chemotherapy in the APML4 study compared to those reported for ATO+ATRA in the trial reported by Lo-Coco 2013, and that this is not unexpected, given that ATO is added to ATRA+chemotherapy without complete removal of the chemotherapy component of the regimen.
- 6.27 No comparative safety data were available to compare the ATO+ATRA+chemotherapy regimen used in APML4 with ATRA+chemotherapy. Only minimal safety data were provided for APML3.
- 6.28 Data on the long-term toxicity of ATO were not provided. There were minimal data on the use of ATO-containing regimens in paediatric patients.

#### **Benefits/harms**

##### Low-intermediate risk APL

- 6.29 A summary of the comparative benefits and harms for ATO+ATRA versus ATRA+chemotherapy in patients with low-intermediate risk APL is presented in the table below.

Table 7: Summary of comparative benefits and harms for ATO+ATRA and ATRA+chemotherapy (Lo-Coco 2013)

Outcome	ATO+ATRA	ATRA+chemo	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				ATO+ATRA	ATRA+chemo	
<b>Benefits</b>						
Event-free survival rate at 2	72/74	65/76	1.14 (1.03, 1.26)	97.3	85.5	11.8% (3.0%, 20.5%)

Outcome	ATO+ATRA	ATRA+chemo	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				ATO+ATRA	ATRA+chemo	
years(mITT)						
OS rate at 2 years	76/77	72/79	1.08 (1.01, 1.17)	98.7	91.1	7.6% (0.8%, 14.3%)
<b>Harms</b>						
Outcome	ATO+ATRA	ATRA+chemo	RR (95% CI)	Event rate/100 patients <sup>a</sup>		RD (95% CI)
				ATO+ATRA	ATRA+chemo	
Death	1/77	7/79	0.15 (0.02, 1.16)	1	9	-7.6% (-14.3%, -0.8%)
APL DS in induction	15/77	13/79	1.18 (0.60, 2.32)	19	16	3.0% (-9.0%, 15.1%)
Leukocytosis <sup>b</sup> during induction	35/74	19/79	1.97 (1.24, 3.11)	47	24	23.2% (8.5%, 38.0%)
<b>Thrombocytopenia grade 3-4<sup>c</sup></b>						
Induction	59%	88%	0.67	59	88	-29%
Consolidation (av. of 3 cycles)	5.0%	32.7%	0.15	5	33	-28%
<b>Neutropenia grade 3-4<sup>d</sup></b>						
Induction	46%	79%	0.58	46	79	-33%
Consolidation (av. of 3 cycles)	5.3%	45.3%	0.12	5	45	-40%
Hepatotoxicity grade 3-4	43/68	4/69	10.91 (4.14, 28.73)	63	6	57.4% (44.7%, 70.2%)
Prolongation of QTc interval	12/77	0/79	-	16	0	15.6% (7.5%, 23.7%)
Gastrointestinal grade 3-4	4.4%	9.9%	0.44	4	10	-6%
Oral toxicity grade 3-4	0	19.4%	-	0	19	-19.4%

<sup>a</sup> Median duration of follow-up: 24.4 months (range 0.5-55.8 months)

<sup>b</sup> defined as WCC>10x10<sup>9</sup>/L

<sup>c</sup> defined as WCC>10x10<sup>9</sup>/L, lasting > 15 days

<sup>d</sup> defined as Platelets <50x10<sup>9</sup>/L; Neutrophil count <1x10<sup>9</sup>/L, lasting > 15 days

Abbreviations: APL DS = acute promyelocytic leukaemia differentiation syndrome; ATO = arsenic trioxide; ATRA = all-trans retinoic acid; chemo = chemotherapy; CI = confidence interval; RD = risk difference; RR = relative risk

Note: Only percentages were available for some safety data and the number of patients included in the analysis set was unclear. In these cases, confidence intervals have not been presented.

Source: Compiled during the evaluation

6.30 On the basis of direct evidence (Lo-Coco 2013) presented by the submission, for every 100 low-intermediate risk APL patients treated with ATO+ATRA in comparison to ATRA+chemotherapy:

- Approximately 12 additional patients would have survived without experiencing an event of treatment failure at 2 years (See Table B.5.1 for definition of treatment failure).
- Approximately 8 additional patients would have survived at 2 years.
- Approximately 3 additional patients would have experienced APL differentiation syndrome during induction.
- Approximately 23 additional patients would have experienced leukocytosis during induction.

- Approximately 29 fewer patients would have experienced prolonged grade 3-4 thrombocytopenia during induction, and approximately 28 fewer patients would have experienced grade 3-4 thrombocytopenia during consolidation therapy over a median duration of follow-up of 34 months.
- Approximately 33 fewer patients would have experienced prolonged grade 3-4 neutropenia during induction, and approximately 40 fewer patients would have experienced grade 3-4 neutropenia during consolidation therapy over a median duration of follow-up of 34 months.
- Approximately 57 additional patients would have experienced prolongation of the QTc interval over a median duration of follow-up of 34 months.
- Approximately 6 fewer patients would have experienced grade 3-4 gastrointestinal toxicity, and 19 fewer patients would have experience grade 3-4 oral toxicity over a median duration of follow-up of 34 months.

#### High risk APL

- There was no direct or indirect evidence presented to assess the safety of ATO+ATRA+chemotherapy relative to ATRA+chemotherapy in high risk APL. The relative benefits/harms of these two alternative treatment regimens in high risk APL patients could not be determined.

#### **Clinical claim**

##### Low-intermediate risk APL

- 6.31 In newly diagnosed patients with low-intermediate risk APL, the submission described a regimen of ATO+ATRA, without chemotherapy or maintenance therapy, as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety relative to a regimen of ATRA+chemotherapy regimen, including maintenance therapy.
- 6.32 The ESC considered that this claim was adequately supported in regard to the comparative effectiveness and short-term safety of the specific regimens compared in Lo-Coco 2013. No long-term safety data were available.

##### High risk APL

- 6.33 In newly diagnosed patients with high risk APL, the submission described a regimen of ATO+ATRA+chemotherapy as superior in terms of comparative effectiveness over a regimen of ATRA+chemotherapy, with maintenance therapy included as part of standard therapy for both proposed and comparator regimens. The submission stated that the addition of ATO to ATRA+chemotherapy resulted in more frequent prolongation of the QTc interval and liver function abnormalities.
- 6.34 The ESC considered that the claim that the ATO+ATRA+chemotherapy regimen is superior in terms of comparative effectiveness to ATRA+chemotherapy for the treatment of newly diagnosed patients with high risk APL was not *strongly* supported.
- 6.35 No direct or indirect comparative safety data were available to assess the treatment regimens proposed for patients with high risk APL.

## **Economic analysis**

- 6.36 The submission presented a modelled cost-effectiveness analysis, in which the treatment effects were based on an unadjusted indirect comparison of two single-arm studies (APML4 and APML3) including both low-intermediate and high risk patients. Results were extrapolated beyond the study duration to a lifetime. As noted earlier, the treatment regimen in APML4 was only relevant to the regimen proposed for the high risk APL patient subgroup. APML3 may not represent the current non-ATO based treatment regimen for APL and the treatment protocol appears less intensive than regimens recommended in current guidelines. As the model was based on an indirect comparison of these two single-arm studies for a combined APL population, the results have limited relevance in the situation where different regimens should be used to treat each of the APL risk-stratified populations (as is usual practice).
- 6.37 The submission provided a sensitivity analysis based on data from Lo-Coco 2013 for the low-intermediate risk patients in the intervention arm, but keeping the treatment effect observed from APML3 in the comparator arm, irrespective of the risk classification. This comparison was not appropriate. Given that the treatment regimen in the intervention arm of Lo-Coco 2013 was consistent with the proposed regimen for low-intermediate patients, and the regimen in the comparator arm was consistent with that recommended in NCCN guideline for the low-intermediate risk subgroup, the economic evaluation based on Lo-Coco 2013 was more appropriate for the low-intermediate risk APL patients and has been referred to as 'alternative base case' in the Commentary. In the alternative base case, high risk APL patients have been excluded from consideration, since no comparative data for this particular subgroup were available. The ESC agreed with the Commentary that the alternative base case was a more appropriate basis for estimating the cost-effectiveness of ATO in the requested PBS population.
- 6.38 The economic model was structured as a Markov state-transition model, with three health states: event-free, relapse/treatment failure and death. A fourth 'tunnel' health state of 'treatment initiation' exists only for the first cycle. The model structure is summarised below.

**Table 8: Summary of model structure and rationale**

Time horizon	Life time (50 years ) in the model base case compared with median follow-up of 34.4 months in Lo-Coco 2013 (alternative base case) and of 4 years in the APML studies (submission base case)
Outcomes	Life years gained (LYG) and quality-adjusted life years gained (QALYs)
Methods used to generate results	Cohort Expected value analysis
Cycle length	1 month
Transition probabilities	Transition probabilities from event-free to failure/relapse, and to death due to APL, were taken from APML4 for the intervention arm, and APML3 for comparator. The alternative base case uses event-free survival and OS from the Lo-Coco 2013 trial. Transition probabilities from treatment failure/relapse to death were sourced from the literature.
Discount rate	5% for costs and outcomes
Software package	TreeAge 2013

APL = acute promyelocytic leukaemia, OS = overall survival  
Source: compiled during the evaluation

6.39 The key drivers of the model are summarised below.

**Table 9: Key drivers of the model**

Description	Method/Value	Impact
Event-free survival and OS	The submission used event-free and overall survival data from APML4 and APML3 for the proposed and comparator regimens respectively, regardless of risk classification.	High, favours ATO+ATRA±Chemo
Time horizon	The submission used a 50 year time horizon in the base case	Moderate, favours ATO+ATRA±chemo
Wastage of pharmaceuticals	The submission assumed no wastage in dispensing pharmaceuticals	Moderate, favours ATO+ATRA±chemo
Setting of IV administration	The submission assumed that all IV administrations would occur in an outpatient setting.	Moderate, favours ATO+ATRA±chemo

OS = overall survival; IV = intravenous; ATO = arsenic trioxide; ATRA = all-trans retinoic acid; chemo = chemotherapy.  
Source: compiled during the evaluation

6.40 The submission stated that in the absence of quality of life data in patients with APL or in the broader category of acute myelocytic leukaemia, the primary analysis presented was measured in incremental cost per life-year gained.

6.41 The results of the economic evaluation presented in the submission and that of the alternative base case conducted during the evaluation are summarised below.

**Table 10: Results of the economic evaluation**

Component	ATO+ATRA±chemotherapy	ATRA+chemotherapy	Increment
<b>Submission base case</b>			
Costs	\$ [REDACTED]	\$63,924	\$ [REDACTED]
LYG	15.57	13.18	2.39
<b>Incremental cost/extra LYG</b>			\$ [REDACTED]
<b>Alternative base case for low-intermediate risk APL only</b>			
Costs	\$ [REDACTED]	\$48,067	\$ [REDACTED]
LYG	16.26	14.62	1.64
<b>Incremental cost/extra LYG</b>			\$ [REDACTED]

ATO = arsenic trioxide; ATRA = all-trans retinoic acid; LYG = life year gained.

Source: Compiled during the evaluation.

- 6.42 As noted earlier, the results of the economic evaluation presented in the submission (based on the APML studies) were of limited relevance to the proposed PBS population, given that the results were for all APL patients, irrespective of risk classification. The treatment regimens in APML4 were only relevant to high risk patients. The appropriateness of using the regimens in APML3 as a comparator is open to debate.
- 6.43 The ESC considered that an economic evaluation for the use of ATO in low-intermediate risk patients based on the results from Lo-Coco 2013 (alternative base case, ICER/LYG \$15,000- \$45,000) was more appropriate.
- 6.44 The ESC noted that treatment-related adverse events were not considered in either the submission's base case or in the alternative base case. This biased the results in favour of the proposed treatment regimens, particularly for the high risk patients.
- 6.45 Sensitivity analyses around the alternative base case indicated that the model was moderately sensitive to the duration of the time horizon, costs of pharmaceutical drugs and drug administration costs.

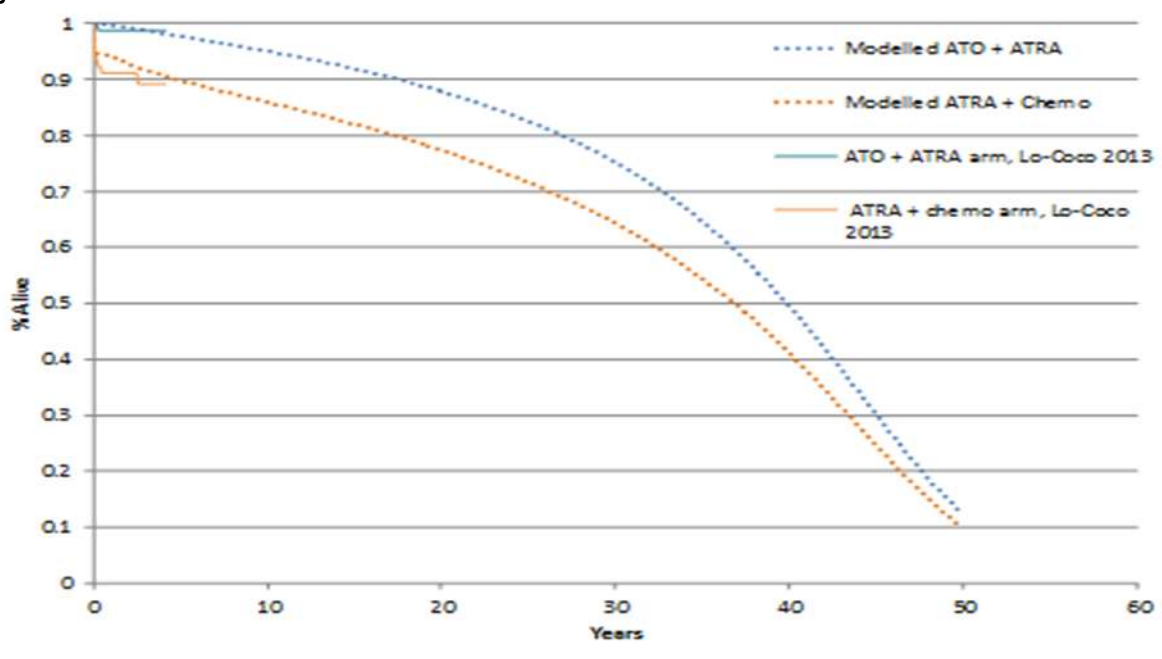
**Table 11: Results of sensitivity analyses around the alternative basecase**

Analysis	Inc. Costs	Inc. LYG	Cost/LYG
Alternative Base case	\$████	1.64	\$████
<b>Wastage associated with Arsenic Trioxide (no wastage in base case)</b>			
Assuming all patients receive 2 vials per day (base case average 1.2 vials per day)	\$████	1.64	\$████
Assuming 70% of patients weigh more than 67kg and receive 2 vials per day (average 1.7 vials per day)	\$████	1.64	\$████
Assuming 50% of patients weight more than 67kg and receive 2 vials per day (average 1.5 vials per day)	\$████	1.64	\$████
<b>Administration Costs (base case: all outpatient setting, \$200 / administration)</b>			
Assuming that 48% of publicly treated patients are treated as an inpatient (average cost per administration \$320)	\$████	1.64	\$████
Assuming that 48% of publicly treated patients are treated as an inpatient, and 100% of private patients are treated as an inpatient (average cost per administration \$403)	\$████	1.64	\$████
Assuming all patients are treated in an inpatient setting (average cost per administration \$531)	\$████	1.64	\$████

Source: Calculated by ESC

- 6.46 The following figure highlights that the survival benefit may be overestimated in the alternative base case. The absolute 10% difference in the surviving proportion is maintained for almost 40 years, and given a mean starting age in the model of 44 years, almost 15% of intervention patients are still alive at age 95 years.

**Figure 1: Survival as demonstrated in Lo-Coco 2013 and as modelled in the submission**



Source: Constructed by ESC

**Drug cost/patient/course:**

- \$ [REDACTED] for low-intermediate risk patients, based on the average time to remission during induction, and protocol duration for the consolidation phases, from Lo-Coco 2013; and
- \$ [REDACTED] for high risk patients, based on the protocol regimen described in APML4.

**Estimated PBS usage & financial implications**

6.47 This submission was not considered by DUSC.

6.48 The submission used an epidemiological approach to estimate the expected financial impact of listing ATO as first-line therapy for APL. The submission used the number of incident cases of APL for the years 1994-1999, obtained from the Australian Institute of Health and Welfare (AIHW) National Cancer Statistics Clearing House. These data, in conjunction with population statistics from the Australian Bureau of Statistics (ABS), were used to estimate the number of incident cases of APL over the first five years of an extended ATO listing on the PBS. The submission stated that, as the proposed ATO+ATRA±chemotherapy regimens were already in use in clinical practice, no changes in the use or cost of other drugs were anticipated.

6.49 The 6th Community Pharmacy Agreement which took effect on 1 July 2015, made some changes to the way chemotherapy preparation fees are paid under the Section 100 Efficient Funding of Chemotherapy (EFC) arrangement.

In addition, some chemotherapy compounders will be paid a smaller fee and the DPMA that is published in the schedule will only include that smaller fee.

Under the finalised new arrangements:

- a) The preparation fees paid to compounders who are licensed by the TGA to undertake such compounding are higher than those paid to compounders who are not licensed by the TGA, recognising that TGA licensed compounders incur additional costs in complying with the TGA's licensing requirements, as compared to chemotherapy compounders who are not TGA licensed;
- b) The preparation fee paid to TGA licensed compounders remains the same as under the 5th CPA at \$102.67\* (indexed price for 2014/2015);
- c) The preparation fees paid to a s90 Community Pharmacy (incl s92 approved practitioners) and a s94 Approved Private Hospital Authority are the same as those paid to TGA licensed compounders to recognise the specialist nature of preparing chemotherapy medicines;
- d) The preparation fee paid to non-TGA licensed compounders is \$20 less at \$82.67.
- e) Where applicable, the \$20 portion of the preparation fee will be paid directly to the compounder through Australian Healthcare Associates (AHA); and.
- f) The \$20 is not currently captured by the DMPA that is published in the Schedule of Pharmaceutical Benefits.

As the majority of chemotherapy preparations are compounded in settings where the \$102.67 fee applies, this fee should continue to be used in PBAC submissions.

- 6.50 Based on the claim that ATO+ATRA±chemotherapy was already standard care in most treatment centres in Australia, the submission’s financial estimates assumed that listing of ATO on the PBS would simply result in a cost shift from hospitals to the PBS. This was reasonable as long as the listing of ATO does not change current clinical management of APL.
- 6.51 The PSCR (p5) presented updated incidence figures for APL. The impact of these updates on the estimated use and financial implications has been presented in the table below.

**Table 12: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients treated					
Base-case					
Revised number of patients					
<b>Total cost to PBS/RPBS<sup>a</sup></b>					
<b>Updated incidence data</b>					
Patient co-payments <sup>b</sup>					
<b>Net cost to PBS/RPBS</b>					
<b>Updated incidence data</b>					

APL = acute promyelocytic leukaemia; ATO = arsenic trioxide

<sup>a</sup> Average dispensed price per prescription \$

<sup>b</sup> Consistent with the Efficient Funding of Chemotherapy Drugs, patients pay only one PBS co-payment for each original prescription dispensed but not for repeat prescriptions.

*The redacted table above shows that the number of patients treated with arsenic trioxide is estimated to be less than 10,000 per year at a net cost to the PBS of less than \$10 million per year.*

- 6.52 The main sources of uncertainty in the estimated net cost to the PBS were:
- The assumption that all patients newly diagnosed with APL would be treated with an ATO-containing regimen, and that the ATO+ATRA±chemotherapy regimens used would be those proposed in the submission;
  - The submission did not allow for wastage, which would underestimate the cost of ATO to the PBS.
- 6.53 The PBAC noted the acknowledgement in the pre-PBAC response that the economic analysis presented in the submission did not appropriately allow for wastage and agreed with the pre-PBAC response that the sensitivity analysis presented in the ESC advice, whereby all patients received two vials of ATO per administration, would overestimate the actual wastage.

### Quality Use of Medicines

- 6.54 The submission stated that as Phenasen<sup>®</sup> was registered with the TGA, the manufacturer of ATO raw material was required to have demonstrated compliance

with Good Manufacturing Practice (GMP), and the final parenteral product must comply with the Guide to GMP for Medicinal Products. In contrast, when products were compounded in hospital pharmacies (as has occurred in some instances in Australia), neither the supplier of the active ingredient nor the manufacturer of the final product needed to be licensed and audited.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the extension of the current listing of arsenic trioxide to include the first line treatment of patients with acute promyelocytic leukaemia (APL). The recommendation was made on the basis the cost-effectiveness of arsenic trioxide in combination with ATRA+/-chemotherapy over ATRA+chemotherapy alone.
- 7.2 The PBAC considered a single listing covering both low-intermediate and high risk patients would be most appropriate, and that the requirement for the t(15:17) translocation or PML/RAR- $\alpha$  gene expression should remain in the restriction. The PBAC noted that, for most patients, results of the gene testing should be received within 24 hours and that pre-treatment with ATRA is standard and would be initiated in the meantime.
- 7.3 The PBAC agreed with the sponsor's request that relapsed patients should be eligible for treatment under the revised restriction, noting that very few patients would relapse and that the lack of data in this patient group is likely due to this low risk of relapse. The PBAC also agreed that the use of ATRA should not be specified in the restriction.
- 7.4 The PBAC agreed that ATRA+chemotherapy was the appropriate main comparator. The PBAC considered that the ATRA+chemotherapy regimens recommended in current clinical guidelines for APL, including the comparator regimen in Lo-Coco 2013, would provide a more relevant comparison than the comparator regimen used in the submission (study APML3).
- 7.5 The PBAC acknowledged the limitations of the data available for the submission, including that the main analysis of effectiveness in the submission was based on a comparison of two single arm studies, APML3 and APML4, and the concerns about the relevance of the comparator regimen used in APML3. The PBAC noted that the evidence presented in the submission and in the PSCR consistently showed that the use of ATO was associated with an improvement in clinical outcomes in low-intermediate and high-risk patients. Therefore, overall, and in the context of APL being a rare condition, the PBAC considered that the comparison presented provided sufficient evidence to support the claim of superior efficacy of ATO with ATRA+/-chemotherapy over ATRA+chemotherapy alone.
- 7.6 In terms of the main comparison presented in the submission, the PBAC noted that all survival endpoints in APML4 (with ATO) were statistically significantly superior to the results of APML3 (without ATO).
- 7.7 The PBAC noted that in APL if relapse occurs it is likely to be soon after treatment,

and in this context considered that event-free survival at 2 years and overall survival at 2 years were appropriate outcomes for assessing efficacy.

- 7.8 In regard to data supporting the use of ATO in paediatric patients, the PBAC noted the availability of results from INT0129: Gregory J, Kim H, Alonzo T, et al: Treatment of children with acute promyelocytic leukemia: results of the first North American Intergroup trial INT0129. *Pediatr Blood Cancer* 53:1005-10, 2009, which showed similar efficacy in children as in adults.
- 7.9 The PBAC noted that, in the short term, treatment with ATO is associated with an increase in cardiac toxicity and hepatotoxicity, but that most of the severe adverse events in the studies were manageable. The PBAC noted that long term toxicity of ATO remains unknown.
- 7.10 The PBAC agreed that Lo-Coco 2013 was appropriate basis for the economic evaluation in low-intermediate risk patients, given that the treatment regimen in this study best represented current clinical management of APL.
- 7.11 The PBAC considered that the life time (50 years) time horizon of the model was appropriate given the high remission rate of treatment and the age of patients at treatment.
- 7.12 The PBAC considered that the ICER was at the high end of what would be considered cost effective, but that this was acceptable in the context of a relatively small population with a high clinical need for this treatment.
- 7.13 The PBAC noted the statement in the pre-PBAC response that ATO administered to inpatients at a public hospital would not be funded through PBS, and that it was therefore appropriate that these costs were not included in the financial estimates.
- 7.14 The PBAC noted that moving to first line treatment would significantly increase the number of patients for whom ATO would be subsidised, the PBAC advised the Department that a reduced price should be sought on this basis. The PBAC noted the assumption in the submission that the listing of ATO on the PBS would result in a cost shift from hospitals to the PBS, and agreed that this was reasonable as long as the listing does not change current clinical management of APL.
- 7.15 The PBAC advised that under subsection 101 (3BA) of the National Health Act 1953, that arsenic should not be treated as interchangeable on an individual patient basis with any other drug.
- 7.16 The PBAC advised that arsenic is not suitable for prescribing by nurse practitioners as antineoplastic agents are currently considered to be out of scope for prescribing by nurse practitioners.
- 7.17 The PBAC recommended that the Safety Net 20 Day Rule should not apply.
- 7.18 The submission is not eligible for an Independent Review, because the PBAC has made a positive recommendation.

**Outcome:**

Recommended

**8 Recommended listing**

8.1 Amend existing listing as follows:

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Proprietary Name and Manufacturer
ARSENIC TRIOXIDE 10mg/ml injection, 10x10mL vials	18mg	140	PHENASEN <sup>®</sup> Phebra
<b>Treatment phase: Induction and consolidation</b>			
Condition	Acute promyelocytic leukaemia		
Restriction	Authority Required (STREAMLINED)		
Clinical criteria	The condition must be characterised by the presence of the t(15:17) translocation or PML/RAR-alpha fusion gene transcript		

**9 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.

**10 Sponsor's Comment**

Phebra welcomes the PBAC's recommendation to extend the PBS listing of Phenasein Injection to include the first line treatment of patients with APL.