AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Arsenic trioxide in combination with all-trans retinoic acid for the first-line treatment of high-risk acute promyelocytic leukaemia in adult patients unsuitable for anthracycline-based therapy (OW06)

September 2023

ONE WALES INTERIM DECISION

Arsenic trioxide in combination with all-trans retinoic acid for the first-line treatment of high-risk acute promyelocytic leukaemia in adult patients unsuitable for anthracycline-based therapy

Date of original advice: October 2016
Date of review: July 2023

The following One Wales Medicines Assessment Group (OWMAG) recommendation has been noted by the All Wales Medicines Strategy Group (AWMSG) and ratified by Welsh Government

Arsenic trioxide in combination with all-trans retinoic acid can be made available within NHS Wales for the first line treatment of high-risk acute promyelocytic leukaemia, characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha gene, in adult patients unsuitable for anthracycline-based therapy.

The risks and benefits of the off-label use of arsenic trioxide for this indication should be clearly stated and discussed with the patient to allow informed consent.

Providers should consult the relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after 3 years or earlier if new evidence becomes available.

Clinician responsibility
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Medicines Assessment Group decision.

Health board responsibility
Health boards will take responsibility for implementing One Wales Medicines Assessment Group decisions and ensuring that a process is in place for monitoring clinical outcomes.

One Wales advice promotes consistency of access across NHS Wales.

This is a summary of new evidence available and patient outcome data collected, to inform the review

Background: Acute promyelocytic leukaemia (APL) is a distinct subtype of acute myeloid leukaemia (AML) and presents clinically with coagulation disorders, which are associated with life threatening haemorrhages. Arsenic trioxide is recommended for use in adult patients with newly diagnosed low-to-intermediate risk APL by the National Institute for Health and Care Excellence (NICE). Treatment of high-risk APL (white blood cell count of >10 × 10^9/L) remains off-label and is currently supported by One Wales interim advice. Clinicians in Wales consider treatment to meet an unmet need and is a potentially curative option for a very small patient group.

Current One Wales decision: The concentrate for solution for infusion formulation is supported for use for this indication.

Licence status: Arsenic trioxide is not currently licensed to treat high risk, front line APL in adults; its use in this indication is off-label. AWTTC is not aware of any plans to pursue marketing authorisation of arsenic trioxide for this indication at this time.

Guidelines: There have been no new relevant guidelines or relevant updates to existing guidelines identified.

Licensed alternative medicines or Health Technology Assessment advice for alternative medicines: none. The NICE appraisal [ID3864] of oral azacitidine for treating relapsed or refractory angioimmunoblastic T-cell lymphoma was discontinued in December 2022 after the applicant company advised that marketing authorisation for this indication was no longer being pursued.

Effectiveness: A repeat literature search undertaken by AWTTC identified a randomised multicentre non-inferiority phase III study (Wang *et al* 2022) to compare the efficacy of all trans retinoic acid and arsenic trioxide (ATRA-ATO) and ATRA-ATO plus chemotherapy in newly diagnosed all-risk APL. In total 128 APL patients were assigned to receive ATRA-ATO for induction, consolidation, and maintenance or ATRA-ATO plus chemotherapy induction therapy followed by three cycles of consolidation therapy with ATRA-ATO plus chemotherapy and maintenance therapy with ATRA-ATO for 6–10 cycles. The trial was designed to evaluate the noninferiority in disease free survival (DFS) after two years following induction therapy. DFS was defined as the time from haematological complete remission to either haematological or molecular relapse or death from APL. The primary end point was event-free survival (EFS) and DFS at 2 years. Secondary endpoints included overall survival (OS) at 2 years. Two-year DFS was 98% in the ATRA-ATO group and 97% in the ATRA-ATO plus chemotherapy group (P = 0.62). The percentage difference in DFS between the two groups was 1.4% (95% CI: 3.8–6.8). The lower limit of the 95% CI for the percentage difference in DFS was greater than the −10% non-inferiority margin, confirming non-inferiority. Of the 128 patients, 21 patients in the non-chemotherapy group and 19 patients in the chemotherapy group had high-risk APL. For high-risk patients, the 2-year DFS was 94% and 87% in the ATRA-ATO treatment regimen compared to ATRA-ATO plus chemotherapy, respectively (P = 0.52). The EFS and OS for high-risk APL patients were 85% and 85% in the non-chemotherapy group versus 78% and 83% in the chemotherapy group (P = 0.44 and 0.96,

respectively). Complete remission was achieved in 90% of high-risk patients in the non-chemotherapy group versus 89% in the chemotherapy group.

Safety: In Wang *et al* 2022, ATRA-ATO was generally better tolerated than ATRA-ATO plus chemotherapy (all-risk patient groups). Most severe adverse events occurred during induction therapy. Grade 3–4 neutropenia and thrombocytopenia lasting more than 15 days occurred more commonly in the chemotherapy group than the non-chemotherapy group, although this did not reach statistical significance (45% versus 32%, P = 0.13). There was also a significantly higher proportion of patients experiencing Grade 3–4 cardiac toxicity in the chemotherapy group vs the non-chemotherapy group (12% versus 2%, P = 0.03).

Cost-effectiveness: No relevant cost-effectiveness analyses identified in the repeat literature search.

Budget impact: The estimated eligible population reported in the original evidence status report was five patients per year in Wales. Since the last review in July 2021, AWTTC is aware of [CONFIDENTIAL DATA REMOVED]

Impact on health and social care services: No new impact data have been provided, though we consider the impact of this medicine to be minimal.

Patient outcome data: In Cardiff and Vale University Health Board [CONFIDENTIAL DATA REMOVED]. Data from the remaining health boards have not been provided.

Evaluation of evidence
We identified one randomised multi-centre non-inferiority phase III study comparing treatment regimen of arsenic trioxide and all-trans retinoic acid with a regimen also including chemotherapy which concluded there was non-inferiority between the regimens. Outcome data show that the treatment has been of benefit and that the budget impact may be lower than originally estimated as fewer patients than predicted are receiving treatment. AWTTC recommends continuing to allow access in Wales to arsenic trioxide in combination with all-trans retinoic acid for the first line treatment of high-risk acute promyelocytic leukaemia.

Next review date: July 2026

References: a full reference list is available on request.

This document includes evidence published since the last review or full assessment of this medicine for the indication under consideration. It does not replace the original full evidence status report. Any previous reviews and the original full evidence status report are available on request by email to AWTTC@wales.nhs.uk.

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Assessment (EHIA) has been completed in relation to the One Wales policy and this found there to be a positive impact. Key actions have been identified and these can be found in the One Wales Policy EHIA document.

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