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 2021

ONE WALES INTERIM COMMISSIONING 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: September 2016
Date of review: July 2021

Arsenic trioxide in combination with all-trans retinoic acid can continue to 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.

Arsenic trioxide is not licensed to treat this indication and is therefore off-label. Each provider organisation must ensure all internal governance arrangements are completed before this medicine is prescribed.

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 2 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 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 assists consistency of access across NHS Wales and will be disseminated to the service following agreement of Health Board Chief Executives.

This is a summary of new evidence available and patient outcome data collected, to inform the 2021 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 was licensed in November 2016 in combination with all-trans retinoic acid (ATRA) for the induction of remission, and consolidation in adult patients with newly diagnosed low-to-intermediate risk APL (white blood cell count ≤ 10 x 10^9/L), characterised by the presence of the t(15;17) translocation and/or the presence of the pro-myelocytic leukaemia/retinoic acid receptor-alpha (PML-RARA) gene[1]. Arsenic trioxide is recommended for use in this indication by the National Institute for Health and Care Excellence (NICE)[2]. Treatment of high-risk APL remains off-label and is currently supported by One Wales interim advice[3]. 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
Arsenic trioxide in combination with all-trans retinoic acid can continue to 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. Reviewed July 2020[3].

Licence status
Arsenic trioxide in combination with ATRA for the first-line treatment of high-risk APL in adult patients remains off-label.

Guidelines
There have been no new guidelines or updates to existing guidelines identified that would affect the current One Wales decision.

Licensed alternative medicines/Health Technology Appraisal advice for alternative medicines
No alternative licensed medicines or health technology appraisal advice for this indication have become available since the last review.

Efficacy/Effectiveness
A repeat literature search identified one retrospective study that investigated the indication and treatment regimen under review.

Min et al (2020) investigated the safety and efficacy of first-line arsenic trioxide and ATRA in high-risk APL adult patients unsuitable to receive anthracycline-based chemotherapy (n = 25) in this single centre study[4]. Median patient age was 66 years (range 30–77). Cumulative incidence of early mortality rate, the primary outcome, was 4% with median follow-up of 21 months (range 0.2–131). One patient died of septic shock two days after arsenic trioxide treatment had started. The remaining patients had either a complete cytogenetic response (n = 17) or a complete molecular response (n = 7) and the majority continued to consolidation treatment (n = 23). Major haematological adverse events included neutropenia (44%), thrombocytopenia (28%) and infectious complications plus fever of unknown origin (32%). Other major adverse events included hepatopathy (32%), differentiation syndrome (24%) and QTc prolongation (28%)[4].

Safety
No new significant safety issues were identified.

Cost effectiveness
A repeat literature search found no new cost-effectiveness evidence to that provided in the original evidence status report.

Budget impact
[CONFIDENTIAL DATA REMOVED] All responding clinicians commented on the usefulness of having this medicine combination funded for this rare cohort of patients in Wales.

Impact on health and social care services
No new information has been provided.

Patient outcome data
[CONFIDENTIAL DATA REMOVED

References

1. European Medicines Agency. Trisenox®. Procedural steps taken and scientific information after the authorisation. May 2017. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000388/WC500042843.pdf. Accessed Jun 2021.
2. National Institute for Health and Care Excellence. Technology Appraisal 526. Arsenic trioxide for treating acute promyelocytic leukaemia. Jun 2018. Available at: https://www.nice.org.uk/guidance/ta526. Accessed Jun 2021.
3. All Wales Therapeutics and Toxicology Centre. One Wales Interim Commissioning Decision. Arsenic trioxide (TRISENOX®) in combination with all-trans retinoic acid for the first-line treatment of acute promyelocytic leukaemia in adult patients unsuitable for anthracycline-based therapy. Jul 2020. Available at: https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-appraisals/one-wales-arsenic-trioxide-for-leukaemia/. Accessed Jun 2021.
4. Min GJ, Cho BS, Park SS et al. Safety and efficacy of arsenic trioxide and all-trans retinoic acid therapy in acute promyelocytic leukemia patients with a high risk for early death. *Annals of Hematology.* 2020;99:973-982. Available at: https://doi.org/10.1007/s00277-020-04010-9. Accessed Jun 2021.