**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal**

# Arsenic trioxide for treating acute promyelocytic leukaemia

**Final scope**

## Remit/appraisal objective

To appraise the clinical and cost effectiveness of arsenic trioxide within its marketing authorisation for the treatment of acute promyelocytic leukaemia.

## Background

Acute promyelocytic leukaemia is a subcategory of acute myeloid leukaemia. In both acute myeloid leukaemia and acute promyelocytic leukaemia, the production of blood cells in the bone marrow results in the development of abnormal cells. In acute promyelocytic leukaemia, the abnormal cells are white blood cells of the neutrophil type and are known as promyelocytes. These cells do not mature properly leading to a reduction of normal white blood cells in circulation. The accumulation of immature cells in the bone marrow also prevents the production of normal red blood cells and platelets resulting in anaemia, low platelet counts, pale skin or fatigue.[1]

The mutation that causes acute promyelocytic leukaemia involves two genes, the promyelocytic leukaemia (PML) gene on chromosome 15 and the RARA gene on chromosome 17. A swap of genes (translocation) between chromosomes 15 and 17, fuses part of the PML gene with part of the RARA gene. The protein produced from this fused gene is known as PML-RARα, this type of genetic change is not inherited. The PML-RARA gene fusion accounts for up to 98% of cases of acute promyelocytic leukaemia.[1]

There were 2,590 diagnoses of acute myeloid leukaemia and 2,127 deaths in England in 2014.[2] Around 10% of acute myeloid leukaemia cases are acute promyelocytic leukaemia.[3] The average age at diagnosis of acute promyelocytic leukaemia is 40 years compared with 65 years for acute myeloid leukaemia, 80% of people with acute promyelocytic leukaemia are aged between 15 and 55 years. Acute promyelocytic leukaemia can affect younger people but it is less common in people under 10 years of age.

First-line treatment for most people with acute promyelocytic leukaemia involves treatment with the AIDA regimen which involves the use of tretinoin (also known as all-trans-retinoic acid or ATRA) in combination with idarubicin, an anthracycline-based chemotherapy. Treatment with ATRA can induce a complete remission in most people with acute promyelocytic leukaemia. ATRA is used in combination with an anthracycline-based chemotherapy to extend the period of remission. Following induction treatment patients usually have a period of consolidation therapy to further extend the period of remission. Second-line treatment options for people who have relapsed or refractory

acute promyelocytic leukaemia include: Arsenic trioxide (ATO) in combination with ATRA, ATRA, cytarabine and hematopoietic stem cell transplantation (HSCT).[4] Stem cell transplants using a person's own cells (ASCT) or matched donor cells (AlloSTC) can be offered, for people with relapsed or refractory disease who are young and otherwise fit.[5] For people treated with ATO in the second-line setting, consolation with an ASCT or AlloSCT is often considered.

**The technology**

Arsenic trioxide (Trisenox, Teva Pharma B.V.) is a form of naturally occurring arsenic believed to have multiple mechanisms of action including inducing cell death by damaging or degrading the PML/RARα fusion protein in acute promyelocytic leukaemia. It is administered by intravenous infusion.

Arsenic trioxide has a UK marketing authorisation for induction of remission, and consolidation in adult patients with:

- newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤ 10 x 103/µl) in combination with all-trans-retinoic acid (ATRA)
- relapsed/refractory acute promyelocytic leukaemia (APL) (previous treatment should have included a retinoid and chemotherapy) characterised by the presence of the t(15;17) translocation and/or the presence of the promyelocytic leukaemia/retinoic-acid-receptor-alpha (PML/RAR-alpha) gene.

The response rate of other acute myelogenous leukaemia subtypes to arsenic trioxide has not been examined.

| | |
|---|---|
| **Intervention(s)** | Arsenic trioxide (with or without ATRA) |
| **Population(s)** | Adults with:<br>• untreated low-to-intermediate risk acute promyelocytic leukaemia<br>• relapsed/refractory acute promyelocytic leukaemia (APL) |
| **Comparators** | • AIDA regimen (ATRA in combination with idarubicin)<br>• hematopoietic stem cell transplantation (people with relapsed or refractory APL)<br>• best supportive care (people with relapsed or refractory APL) |
| **Outcomes** | The outcome measures to be considered include:<br>• overall survival |

| | |
|---|---|
| | • progression-free survival<br>• response rates (bone marrow remission)<br>• adverse effects of treatment<br>• health-related quality of life. |
| **Economic analysis** | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br>Costs will be considered from an NHS and Personal Social Services perspective. |
| **Other considerations** | Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. |
| **Related NICE recommendations and NICE Pathways** | Related Technology Appraisals:<br>'Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts' (2016). NICE Technology Appraisal 399. Review proposal date July 2019.<br>'Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia' (2011). NICE Technology Appraisal 218. On static list.<br>Terminated appraisals:<br>'Decitabine for the treatment of acute myeloid leukaemia' (terminated appraisal) (2012). NICE Technology Appraisal 270.<br>Related guidelines:<br>'Haematological cancers: improving outcomes' (2016). NICE Guideline 47. Review date to be confirmed.<br>Related NICE Pathways:<br>Blood and bone marrow cancers (2016) NICE pathway |
| **Related National Policy** | **NHS England:**<br>NHS England (2016) Manual for Prescribed Specialised Services 2016/17. Chapters 29 and 105. |

| | |
|---|---|
| | https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf<br><br>**National Service Frameworks:**<br>Cancer<br><br>**Department of health:**<br>Department of Health (2014) The national cancer strategy: 4th annual report<br><br>Department of Health (2011) Improving outcomes: a strategy for cancer<br><br>Department of Health (2009) Cancer commissioning guidance<br><br>Department of Health (2007) Cancer reform strategy<br><br>Department of Health, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1,2 and 3. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 |

**References**


[1] Acute promyeloctyic leukemia, U.S National Library of Medicine, https://ghr.nlm.nih.gov/condition/acute-promyelocytic-leukemia. Accessed June 2017

[2] Cancer Research UK, 2014, Acute myeloid leukaemia (AML) incidence statistics. Accessed June 2017

[3] Genetics Home Reference, 2016, Acute promyelocytic leukemia. Accessed June 2017

[4] ASH Education Book, 2006, Treatment of Acute Promyelocytic Leukemia. Accessed June 2017

[5] Leukaemia Care, 2016, Acute Promyelocytic Leukaemia (APL). Accessed June 2017