

Arsenic trioxide for treating acute promyelocytic leukaemia

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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1 Recommendations

- 1.1 Arsenic trioxide is recommended, within its marketing authorisation, as an option for inducing remission and consolidation in acute promyelocytic leukaemia (characterised by the presence of the t[15;17] translocation or the PML/RAR-alpha gene) in adults with:
- untreated, low-to-intermediate risk disease (defined as a white blood cell count of 10×10^3 per microlitre or less), when given with all-trans-retinoic acid (ATRA)
 - relapsed or refractory disease, after a retinoid and chemotherapy.

Why the committee made these recommendations

People with untreated, low-to-intermediate risk acute promyelocytic leukaemia are given ATRA plus chemotherapy (together called AIDA). Clinical trial evidence shows that arsenic trioxide plus ATRA is effective for untreated disease compared with AIDA. Some assumptions in the model, such as the costs of stem cell transplant and the long-term effect of treatment, lead to the cost-effectiveness analyses being uncertain. However, the most plausible cost-effectiveness estimate is likely to be less than £20,000 per quality-adjusted life year gained, so arsenic trioxide plus ATRA is cost effective compared with AIDA in untreated disease.

Arsenic trioxide is already used to treat relapsed or refractory acute promyelocytic leukaemia. The clinical- and cost-effectiveness evidence for arsenic trioxide in relapsed or refractory disease is uncertain, because the clinical trial was small and did not compare arsenic trioxide with AIDA. However, it is likely that arsenic trioxide is clinically effective and represents a cost-effective use of NHS resources in relapsed or refractory disease. Therefore, arsenic trioxide is recommended for both untreated and relapsed or refractory disease.

2 Information about arsenic trioxide

<p>Marketing authorisation indication</p>	<p>Arsenic trioxide (Trisenox, Teva) is indicated for the induction of remission, and consolidation in adults with:</p> <ul style="list-style-type: none"> newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (white blood cell count $\leq 10 \times 10^3$ per microlitre) in combination with all-trans-retinoic acid (ATRA) relapsed/refractory acute promyelocytic leukaemia (previous treatment should have included a retinoid and chemotherapy) <p>characterised by the presence of the t(15;17) translocation and/or the presence of the PML/RAR-alpha gene.</p>
<p>Dosage in the marketing authorisation</p>	<p>For newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia:</p> <ul style="list-style-type: none"> 0.15 mg/kg per day intravenously. In induction, this is given daily until complete remission or for a maximum of 60 days. In consolidation, this is given 5 days per week for 4 weeks on and 4 weeks off, for a total of 4 cycles. <p>For relapsed and refractory acute promyelocytic leukaemia:</p> <ul style="list-style-type: none"> 0.15 mg/kg per day intravenously. In induction, this is given daily until complete remission or for a maximum of 50 days. Consolidation treatment must begin 3 to 4 weeks after completing induction therapy. In consolidation, treatment is given for 25 doses, 5 days per week, followed by 2 days interruption, repeated for 5 weeks. <p>Treatment with arsenic trioxide must be temporarily stopped before the scheduled end of therapy if a toxicity grade 3 or greater on the National Cancer Institute Common Toxicity Criteria is observed and judged to be possibly related to arsenic trioxide treatment. Treatment may be resumed at 50% of the preceding daily dose after the toxic event is resolved or after recovery to baseline status of the abnormality that prompted the interruption.</p>

Price	£2,920 for 10 ampoules of 10 mg/10 ml concentrate for solution for infusion (excluding VAT; British national formulary [BNF] online [accessed March 2018]). Costs may vary in different settings because of negotiated procurement discounts.
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3 Committee discussion

The appraisal committee ([section 5](#)) considered evidence submitted by Teva and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

New treatment option

People with acute promyelocytic leukaemia would welcome a new treatment option

- 3.1 Acute promyelocytic leukaemia is a rapidly progressing form of leukaemia for which treatment must be started quickly. Symptoms include bruising or bleeding (which can sometimes be catastrophic at presentation because of severely disordered blood clotting), fatigue, feeling weak or breathless, bone or joint pain and sleeping problems. A patient group explained that these symptoms affect mobility and daily living such that they may impair education and employment. Current treatments also have high toxicity. For example, the long-term effects of chemotherapy can include a risk of secondary cancers and loss of fertility in younger people. The committee concluded that people with acute promyelocytic leukaemia would welcome an alternative to chemotherapy that could reduce the chance of relapse.

Clinical management

Untreated acute promyelocytic leukaemia is treated with ATRA plus chemotherapy

- 3.2 Current treatment for untreated, low-to-intermediate risk acute promyelocytic leukaemia is all-trans-retinoic acid (ATRA) with an anthracycline-based chemotherapy (usually idarubicin, a combination known as AIDA). The committee concluded that, for untreated disease, AIDA is the relevant comparator for arsenic trioxide.

Relapsed or refractory acute promyelocytic leukaemia is treated with arsenic trioxide plus ATRA

3.3 Arsenic trioxide, in combination with ATRA, has been used to treat relapsed or refractory acute promyelocytic leukaemia in NHS clinical practice for over 10 years. The committee understood that the marketing authorisation for arsenic trioxide for relapsed or refractory disease does not include combination treatment with ATRA. The clinical expert explained that arsenic trioxide would not be used to treat relapsed or refractory disease without ATRA in clinical practice in England. The marketing authorisation also states that previous treatment should have included a retinoid and chemotherapy. The company stated that the choice of treatment for relapsed or refractory disease is largely determined by the first treatment used; for example, after treatment with AIDA for untreated disease, current practice is to treat relapsed or refractory disease with arsenic trioxide plus ATRA. The company also stated that if arsenic trioxide were recommended for untreated disease, fewer people would go on to have relapsed or refractory disease so the population eligible for arsenic trioxide would shrink over time. The clinical expert explained that because the risk of relapse is so low after using arsenic trioxide, there is little experience in England of treating relapsed or refractory acute promyelocytic leukaemia after arsenic trioxide. Nevertheless, they added that it would be reasonable to offer AIDA after arsenic trioxide for relapsed or refractory disease. The company stated that stem cell transplant would be used after arsenic trioxide in relapsed or refractory disease, rather than instead of it, so it was not a relevant comparator. The company also stated that best supportive care was not a relevant comparator because it would likely only be used when the disease did not respond to all other treatments, including arsenic trioxide. The committee agreed that, for relapsed or refractory disease, AIDA was the relevant comparator for arsenic trioxide.

Population

The relevant population is defined in the marketing authorisation

3.4 The marketing authorisation for arsenic trioxide is for use in adults with

untreated, low-to-intermediate risk acute promyelocytic leukaemia, and in adults with relapsed or refractory acute promyelocytic leukaemia. The committee understood that arsenic trioxide is currently used to treat relapsed or refractory disease in adults. The clinical expert stated that there was no reason to expect that treatment would be less effective in children. The committee was aware of NHS England's policy on [Commissioning Medicines for Children in Specialised Services](#), which states that NHS England will commission treatments for patients aged less than 18 years if specific commissioning conditions within a NICE technology appraisal are met. The committee noted that the marketing authorisation for arsenic trioxide's use in untreated acute promyelocytic leukaemia did not include high-risk disease. The committee concluded that, in line with NICE policy, it would appraise arsenic trioxide for the population defined in its marketing authorisation.

Clinical evidence

The clinical-effectiveness evidence is relevant to NHS clinical practice in England

3.5 The evidence for arsenic trioxide in untreated acute promyelocytic leukaemia came from 2 clinical trials: APL0406 (n=266) and AML17 (n=235). Both studies were phase III, randomised, open-label trials; only AML17 included patients from the UK. Both trials compared arsenic trioxide plus ATRA with AIDA. The committee understood that APL0406 used the dosing schedule and population defined in the marketing authorisation for arsenic trioxide, whereas AML17 used a lower dose (about 60% of that in the marketing authorisation) and included people with high-risk disease. The clinical expert confirmed that in England, arsenic trioxide has been used according to the AML17 protocol. However, the committee agreed that it could only appraise arsenic trioxide within its marketing authorisation. The ERG highlighted that the populations in both trials were similar, which suggested that the population in APL0406 may be similar to the population eligible for arsenic trioxide in England. The committee concluded that APL0406 was relevant to NHS clinical practice in England, and that AML17 was relevant as supporting evidence.

Arsenic trioxide plus ATRA is effective for untreated acute promyelocytic leukaemia

3.6 The primary outcome measure in APL0406 was event-free survival at 2 years after diagnosis. An event was defined as no haematological remission after induction, no molecular remission after 3 consolidation courses, haematological or molecular relapse, or death. Although APL0406 was designed as a non-inferiority trial, the investigators were able to demonstrate the superiority of arsenic trioxide plus ATRA compared with AIDA for some outcomes. The results showed that 97.3% of people in the arsenic trioxide plus ATRA group had not had an event after 50 months, compared with 80.0% in the AIDA group. This difference was statistically significant ($p < 0.001$). More people having arsenic trioxide plus ATRA were alive at 50 months compared with people having AIDA (99.2% compared with 92.6%, $p = 0.007$). There was also a statistically significant ($p = 0.001$) lower cumulative incidence of relapse with arsenic trioxide plus ATRA (1.9%), compared with AIDA (13.9%) at 50 months. The primary outcome in AML17 was health-related quality of life. The results did not show a statistically significant difference between arsenic trioxide plus ATRA and AIDA in most health-related quality of life outcomes, but the committee understood that the study may have been underpowered to detect this difference. At 4 years there was a statistically significant difference in event-free survival (91% with arsenic trioxide plus ATRA and 70% with AIDA; $p = 0.002$) but not in overall survival (93% and 89%; $p = 0.250$). The clinical expert highlighted that an effective monitoring and intervention strategy as part of the trial may have led to improved outcomes in the AIDA group. The committee concluded that arsenic trioxide plus ATRA was effective for untreated acute promyelocytic leukaemia.

The effectiveness of arsenic trioxide for relapsed or refractory disease is uncertain

3.7 The company presented results from a very small randomised trial (Raffoux et al., $n = 20$) that compared arsenic trioxide alone with arsenic trioxide plus ATRA for relapsed or refractory acute promyelocytic leukaemia. The results for cumulative percentage of complete remission, overall survival and disease-free survival were similar in both treatment

groups. The committee noted that the company had not presented evidence for the effectiveness of arsenic trioxide compared with AIDA for relapsed or refractory disease. The company stated that there was little high-quality evidence in relapsed or refractory disease because acute promyelocytic leukaemia is rare, and only around a third of people will have a relapse. The committee agreed that the effectiveness of arsenic trioxide for relapsed or refractory acute promyelocytic leukaemia is uncertain.

Adverse events

The long-term safety of arsenic trioxide remains to be explored

3.8 In APL0406, haematological adverse events were generally less common with arsenic trioxide plus ATRA than with AIDA. However, there was a higher incidence of hepatic toxicity in people having arsenic trioxide plus ATRA than people having AIDA, particularly during induction (40% compared with 3% respectively; $p < 0.001$). Some patients taking arsenic trioxide may experience an abnormality of the heart rhythm (QTc prolongation), but the clinical expert indicated that this was uncommon and that the potential toxicity to heart muscle function from idarubicin, an anthracycline, was of greater concern. The committee noted that the European Medicines Agency had recommended a long-term safety study of arsenic trioxide. The company highlighted that adverse events in the trial were mostly managed by temporarily stopping treatment, and that few people permanently stopped treatment. The committee concluded that the long-term safety of arsenic trioxide remains to be explored.

The company's economic model

The model structure is appropriate for decision-making

3.9 The company presented a single Markov model to assess the cost effectiveness of arsenic trioxide in both untreated and relapsed or refractory acute promyelocytic leukaemia. The model included 14 health states, with additional tunnel states. The first treatment was either

arsenic trioxide plus ATRA or AIDA.

- After first having AIDA, people with relapsed disease had arsenic trioxide plus ATRA.
- After first having arsenic trioxide plus ATRA, people whose disease had been in remission for less than 2 years before relapse had AIDA. People whose disease had been in remission for 2 years or more before relapse had arsenic trioxide plus ATRA again.

The committee noted that this retreatment with arsenic trioxide was not in line with the marketing authorisation, which states that treatment for relapsed or refractory disease should follow a retinoid or chemotherapy. However, it was aware that there is little experience in England of treating relapsed or refractory disease after arsenic trioxide because the risk of relapse is low ([section 3.3](#)), and that the other treatment pathway in the model for people who first had arsenic trioxide plus ATRA was in line with the marketing authorisation. The committee concluded that the model was appropriate for decision-making.

Treatment effectiveness in the model

How treatment effectiveness is implemented in the model leads to uncertainty

- 3.10 In the company's model, the benefit of treatment with arsenic trioxide plus ATRA was maintained for the entire time horizon. For example, the rate of relapse after initial treatment was constant from 2 years after remission until the end of the time horizon. In response to a request from NICE and the ERG at the clarification stage, the company did a scenario analysis in which there were no relapses after 2 years of complete remission following the first treatment. This scenario reduced the cost effectiveness of arsenic trioxide plus ATRA compared with AIDA. The ERG did a further scenario analysis in which it assumed equal relapse probability for both treatment groups after 2 years of complete remission following the first treatment. This scenario also reduced the cost effectiveness of arsenic trioxide plus ATRA compared with AIDA. The

committee agreed that it was unlikely that the benefit of treatment with arsenic trioxide plus ATRA would be maintained for the rest of a person's life. It also agreed it was unlikely that the relapse probability would be equal for both treatment groups after 2 years of complete remission following the first treatment, as in the ERG's scenario. However, the committee was reassured that even in this clinically unlikely scenario, the incremental cost-effectiveness ratio (ICER) was within the range that NICE normally considers to be a cost-effective use of NHS resources. The committee concluded that although the implementation of treatment effectiveness in the model led to uncertainty in the cost-effectiveness results, arsenic trioxide plus ATRA was cost effective compared with AIDA.

Stem cell transplant in the model

The costs associated with stem cell transplant in the model are uncertain

3.11 The committee noted that in the company's base case, the costs of haematopoietic stem cell transplant (HSCT) predicted by the model were £40,681 higher in the AIDA group than in the arsenic trioxide plus ATRA group. This was mainly because more patients in the AIDA group would be expected to have a relapse and subsequently need HSCT. The clinical expert confirmed that in AML17, no patients who had arsenic trioxide plus ATRA had subsequently had a relapse. In the model, the cost of allogeneic HSCT was much higher than the cost of autologous HSCT. There were also substantial yearly costs associated with remission after HSCT, which again were much higher after allogeneic HSCT. The ERG highlighted that in the model, people did not stay in the remission after HSCT health state for more than a few years. The clinical expert stated that costs would realistically be higher for allogeneic HSCT because it is associated with more complications than autologous HSCT, and that the difference in costs predicted by the model seemed reasonable. The committee noted that changing the costs of HSCT in the model had a large effect on the cost-effectiveness results. It considered scenario analyses in which the yearly costs associated with remission after HSCT were set to £5,000 and to £0 per year. The committee agreed it was

unlikely that there would be no costs after HSCT, but was reassured that even in these clinically unlikely scenarios, the ICERs were close to, or within, the range that NICE normally considers to be a cost-effective use of NHS resources. It concluded that although there was uncertainty about the most appropriate costs for HSCT and the costs used in the model led to uncertainty in the cost-effectiveness results, arsenic trioxide plus ATRA was cost effective compared with AIDA.

Cost-effectiveness results

Arsenic trioxide plus ATRA is less costly and more effective than AIDA for untreated disease in the company's analysis

3.12 The company's deterministic base-case results showed that arsenic trioxide plus ATRA was less costly (–£31,270 incremental costs) and more effective (2.62 incremental quality-adjusted life years [QALYs] gained) than AIDA for untreated acute promyelocytic leukaemia.

Arsenic trioxide plus ATRA remains less costly and more effective than AIDA for untreated disease in the ERG's analysis

3.13 The ERG made a number of changes to the company's base case, including:

- correcting errors
- changing the time horizon from 40 to 56 years
- using some alternative utility values
- capping utility values so they did not exceed those of the general population
- using some alternative remission probabilities.

The ERG's base case also showed that arsenic trioxide plus ATRA was less costly (–£23,502 incremental costs) and more effective (2.25 incremental QALYs gained) than AIDA for untreated acute promyelocytic leukaemia. The committee noted that the ERG's scenario analysis assuming equal relapse

probability for both treatment groups ([section 3.10](#)) showed that arsenic trioxide plus ATRA was not cost saving compared with AIDA, with an ICER of £19,734 per QALY gained. However, the committee acknowledged that even in this unlikely scenario, the ICER was within the range that NICE normally considers to be a cost-effective use of NHS resources.

The most plausible ICER for untreated disease is less than £20,000 per QALY gained

3.14 The committee considered another scenario analysis in which, as well as assuming equal relapse probability for both groups, the costs of remission after HSCT were set to £0. This analysis produced an ICER for arsenic trioxide plus ATRA compared with AIDA of £31,042 per QALY gained. The committee considered that this scenario was clinically implausible but was reassured that even in this scenario the ICER was close to the range that NICE normally considers to be a cost-effective use of NHS resources. The committee was not persuaded that arsenic trioxide plus ATRA was cost saving compared with AIDA, but it agreed that arsenic trioxide plus ATRA was cost effective. The committee concluded that although there was uncertainty in the model, the most plausible ICER for arsenic trioxide plus ATRA compared with AIDA for untreated disease was less than £20,000 per QALY gained.

The cost effectiveness of arsenic trioxide in relapsed or refractory disease is difficult to establish given the available data

3.15 The company presented a scenario analysis to assess the cost effectiveness of arsenic trioxide plus ATRA compared with AIDA for relapsed or refractory disease. This analysis produced an ICER for arsenic trioxide plus ATRA compared with AIDA of £16,733 per QALY gained. The ERG noted that it was unclear how this analysis had been done, and presented another scenario analysis based on its own base-case analysis in which it removed the initial treatment health states. This analysis produced an ICER for arsenic trioxide plus ATRA compared with AIDA of £31,184 per QALY gained. Having raised concerns about the lack of evidence in relapsed or refractory disease ([section 3.7](#)), extrapolating treatment effectiveness ([section 3.10](#)) and the costs associated with HSCT ([section 3.11](#)), the committee agreed that these results were

uncertain. It also noted that the model assessed arsenic trioxide plus ATRA, rather than arsenic trioxide alone, as specified in the marketing authorisation for relapsed or refractory disease. It concluded that the cost effectiveness of arsenic trioxide in relapsed or refractory acute promyelocytic leukaemia was difficult to establish given the available data.

Arsenic trioxide is recommended for untreated low-to-intermediate risk acute promyelocytic leukaemia

3.16 The committee agreed that despite uncertainties in the economic model, arsenic trioxide plus ATRA represents a cost-effective use of NHS resources for untreated, low-to-intermediate risk acute promyelocytic leukaemia in adults. The committee was aware that current practice in England is to treat acute promyelocytic leukaemia according to the reduced dosing schedule used in AML17. However, it clarified that its recommendation was to use arsenic trioxide within its marketing authorisation (that is, at the dose specified in the marketing authorisation, and for low-to-intermediate risk disease).

Arsenic trioxide is also recommended for relapsed or refractory acute promyelocytic leukaemia

3.17 The committee acknowledged that there was uncertainty in the evidence for arsenic trioxide for treating relapsed or refractory acute promyelocytic leukaemia. However, arsenic trioxide plus ATRA is current practice in the NHS for treating relapsed or refractory disease. The committee also considered that, because it had recommended arsenic trioxide for use in untreated disease, the number of people eligible for arsenic trioxide for relapsed or refractory disease would fall over time. The committee was reassured by the similar clinical outcomes for arsenic trioxide compared with arsenic trioxide plus ATRA. The committee was also reassured that the ICERs for untreated disease were below the range normally considered to be a cost-effective use of NHS resources, and it considered that arsenic trioxide was likely to be cost effective in relapsed or refractory disease as well. Recognising that its decisions should be constrained to the marketing authorisation ([section 3.4](#)), the committee concluded that it could recommend arsenic trioxide

as an option, within its marketing authorisation, for treating relapsed or refractory acute promyelocytic leukaemia.

End of life

Arsenic trioxide does not meet the criteria to be considered a life-extending treatment at the end of life

3.18 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [Cancer Drugs Fund technology appraisal process and methods](#). The company did not make a case for the end-of-life criteria to apply. The committee noted that after 84 months, median survival was not reached in APL0406, and that the life years predicted in the company's model for people having AIDA were 26.8 years for untreated disease and 10.7 years for relapsed or refractory disease. The committee concluded that arsenic trioxide did not meet the criteria to be considered a life-extending treatment at the end of life.

Other factors

There are no equality issues relevant to the recommendations

3.19 Stakeholders highlighted that older people or people who are Jehovah's witnesses would be eligible for arsenic trioxide. Because arsenic trioxide is recommended for the whole population in the marketing authorisation, the committee concluded that its recommendations do not have a different impact on people protected by the equality legislation than on the wider population. It concluded that there are no relevant equality issues.

There are no additional benefits that are not captured in the QALY calculations

3.20 The company considered arsenic trioxide to be an innovative treatment, because it is an alternative to chemotherapy. A professional group also considered arsenic trioxide to be innovative because it reduces the risk

of relapse and need for HSCT. The committee concluded that arsenic trioxide would be beneficial for patients, but that it had not been presented with evidence of any additional benefits that were not captured in the measurement of QALYs.

4 Implementation

- 4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal determination.
- 4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has acute promyelocytic leukaemia and the doctor responsible for their care thinks that arsenic trioxide is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee C](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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