

Liposomal cytarabine–daunorubicin for untreated acute myeloid leukaemia

Technology appraisal guidance
Published: 19 December 2018

www.nice.org.uk/guidance/ta552

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 Liposomal cytarabine–daunorubicin is recommended, within its marketing authorisation, as an option for untreated therapy-related acute myeloid leukaemia or acute myeloid leukaemia with myelodysplasia-related changes in adults. It is recommended only if the company provides it according to the [commercial arrangement](#).

Why the committee made these recommendations

Current treatment for therapy-related acute myeloid leukaemia and acute myeloid leukaemia with myelodysplasia-related changes is chemotherapy. Clinical trial evidence shows that people having liposomal cytarabine–daunorubicin live longer than people having standard chemotherapy.

Liposomal cytarabine–daunorubicin meets NICE's criteria for being a life-extending treatment at the end of life. Using the most plausible assumptions and the price discount, the cost-effectiveness estimates of liposomal cytarabine–daunorubicin compared with standard chemotherapy are within the range that NICE normally considers a cost-effective use of NHS resources for end-of-life treatments. So liposomal cytarabine–daunorubicin is recommended.

2 Information about liposomal cytarabine–daunorubicin

Marketing authorisation indication

- 2.1 Liposomal cytarabine–daunorubicin (Vyxeos, Jazz Pharmaceuticals) is indicated for 'the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)'.

Dosage in the marketing authorisation

- 2.2 The company's submission states that liposomal cytarabine–daunorubicin is given by intravenous infusion over 90 minutes. The dose is based on the patient's body surface area, according to the following schedule:
- For induction of remission: daunorubicin 44 mg/m² and cytarabine 100 mg/m² on days 1, 3 and 5 for the first course and on days 1 and 3 for subsequent courses, if needed.
 - For consolidation (5 to 8 weeks after the start of the last induction): daunorubicin 29 mg/m² and cytarabine 65 mg/m² on days 1 and 3. A subsequent course of consolidation may be given when there is no disease progression or unacceptable toxicity.

Price

- 2.3 The company stated that the list price of liposomal cytarabine–daunorubicin is £4,581 per 50-ml vial. The company has a [commercial arrangement](#). This makes liposomal cytarabine–daunorubicin available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

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

Potential new treatment option

People with acute myeloid leukaemia that is therapy-related or with myelodysplasia-related changes would welcome a new treatment option

- 3.1 Therapy-related acute myeloid leukaemia and acute myeloid leukaemia with myelodysplasia-related changes are high-risk types of acute myeloid leukaemia with poor survival outcomes. Patient experts described that the most common symptoms include fatigue, feeling weak or breathless, loss of memory and concentration, bruising and bleeding, and nausea or vomiting. They also highlighted that the diagnosis has an emotional and financial effect on patients, and their families and carers. Both the patient and clinical experts explained that patients would welcome a treatment that helps them be well enough to have a stem cell transplant, which is potentially a curative treatment. The committee concluded that people with therapy-related acute myeloid leukaemia and acute myeloid leukaemia with myelodysplasia-related changes would welcome a new treatment that could improve survival, quality of life, and the chance of getting a stem cell transplant.

Clinical management

Current treatment is chemotherapy

- 3.2 Current treatment for therapy-related acute myeloid leukaemia and acute myeloid leukaemia with myelodysplasia-related changes is intensive chemotherapy, for people who are well enough to have it. This usually

involves a first induction course, and 2 or 3 further courses of standard daunorubicin and cytarabine to treat any remaining cancer cells (consolidation therapy). In the NHS, the first induction course is usually given as 3 days of daunorubicin and 10 days of cytarabine (known as DA 3+10). The clinical experts highlighted that some younger patients may have FLAG-Ida (fludarabine, cytarabine, granulocyte-colony stimulating factor and idarubicin) chemotherapy instead. The committee understood that liposomal cytarabine–daunorubicin is a liposomal formulation of standard cytarabine and daunorubicin chemotherapy. This could be used as an alternative in clinical practice. The committee was aware that diagnosing some types of high-risk acute myeloid leukaemia, particularly de novo acute myeloid leukaemia with myelodysplastic syndrome-associated karyotypic changes, involves genetic testing. In England, genetic test results may not be available for 7 to 10 days. The clinical experts advised that it is becoming more common for clinicians to wait for these test results before starting treatment. A small number of patients with more aggressive disease would need to start treatment sooner. The committee agreed that no change in practice would be needed for most people who would be eligible for liposomal cytarabine–daunorubicin, if it were to recommend the treatment. The committee concluded that standard cytarabine and daunorubicin chemotherapy is the relevant comparator for this appraisal.

Clinical evidence

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

- 3.3 The evidence for liposomal cytarabine–daunorubicin came from Study 301. This was a phase 3, multicentre, open-label, randomised trial. It included 309 adults aged 60 to 75 years with high-risk acute myeloid leukaemia. High-risk acute myeloid leukaemia was defined as therapy-related acute myeloid leukaemia, acute myeloid leukaemia with myelodysplastic syndrome, de novo acute myeloid leukaemia with myelodysplastic syndrome-associated karyotypic changes and chronic myelomonocytic leukaemia. The trial compared liposomal cytarabine–daunorubicin (n=153) with standard cytarabine and

daunorubicin chemotherapy (n=156), in a 3+7 schedule (3 days of cytarabine then 7 days of daunorubicin). The clinical experts confirmed that it was reasonable to assume equivalence between the 3+7 schedule in the trial and the 3+10 schedule normally used in the UK. They also confirmed that, although the trial was done in the US and Canada, the baseline characteristics of people in the trial were representative of people in the UK who would be eligible for liposomal cytarabine–daunorubicin. The clinical experts explained that about a quarter of patients who would be eligible for treatment in England would be under 60 years. There was no biological reason to expect treatment benefit to be any different to that seen in people aged 65 to 70 years in the trial. The committee concluded that the clinical-effectiveness evidence from Study 301 was relevant to clinical practice in England.

Liposomal cytarabine–daunorubicin improves overall survival compared with standard cytarabine and daunorubicin

3.4 The primary outcome measure in Study 301 was overall survival. Treatment with liposomal cytarabine–daunorubicin increased median overall survival compared with standard cytarabine and daunorubicin, from 5.95 months to 9.56 months (hazard ratio [HR] 0.69; 95% confidence interval [CI] 0.52 to 0.90, $p=0.005$). The company also presented results from a post-hoc analysis of overall survival from the time of stem cell transplant. Fifty-two people in the liposomal cytarabine–daunorubicin group and 39 people in the standard cytarabine and daunorubicin group had a stem cell transplant and were included in this analysis. Median overall survival was 10.25 months in the standard cytarabine and daunorubicin group and was not reached in the liposomal cytarabine–daunorubicin group (HR 0.46; 95% CI 0.24 to 0.89, $p=0.0046$). The committee noted that there was a plateau in the Kaplan–Meier graphs for the liposomal cytarabine–daunorubicin group at around 6 months after transplant, but not for the standard cytarabine and daunorubicin group. The clinical experts stated that response to transplant may differ depending on the person's health when they had the transplant, but that they would expect to see a plateau from the same time point in both groups. The committee noted that the post-hoc analysis included a small number of patients. It also noted that, in the trial, the decision to transplant was not randomised and therefore there

could be bias in the results of the post-hoc analysis. The committee also noted that the results presented by the company were from a data cut in December 2015, 3 years after the first patient was randomised, although the company stated that trial follow-up was continuing for 5 years after randomisation. Also, after 1 year, a substantial number of patients were censored in the analysis, which the committee agreed made the long-term results more uncertain. In response to consultation, the company presented updated Kaplan–Meier graphs, using safety data up to August 2018. It presented graphs both for overall survival in the full population and from the time of stem cell transplant. The committee agreed that the updated graphs were more reliable because there was less censoring and there was a plateau in both treatment groups. The company suggested that the difference between groups in response to transplant was because people in the liposomal cytarabine–daunorubicin group were in better health before transplant or had less residual leukaemia going into transplant, or both. However, minimal residual disease status before transplant was not collected in the trial. The committee concluded that there was some uncertainty about how much survival was improved after stem cell transplant, but that liposomal cytarabine–daunorubicin improved overall survival in the whole population compared with standard cytarabine and daunorubicin.

Adverse effects

Liposomal cytarabine–daunorubicin is well tolerated

- 3.5 The committee noted that the adverse effects reported in Study 301 were broadly comparable between the 2 groups. The patient expert noted that liposomal cytarabine–daunorubicin had been more tolerable for them than other treatments. The clinical experts suggested that people in the liposomal cytarabine–daunorubicin group of Study 301 may have taken the active treatment for longer, leading to similar rates of adverse effects in the 2 groups, rather than lower rates in the liposomal cytarabine–daunorubicin group as they may have expected. The committee concluded that liposomal cytarabine–daunorubicin was generally well tolerated.

The company's economic model

The model is appropriate for decision making but there is uncertainty in extrapolating overall survival after transplant and the cure fraction used

3.6 The company presented an economic model in 2 parts: an initial decision tree to determine if patients were in remission after induction therapy, and whether they had a stem cell transplant or not, and then subsequent partitioned survival models. The model had a 30 year time horizon. This was assumed to be a lifetime time horizon because patients in the model were 60 to 75 years, as in Study 301. To extrapolate beyond the trial period, the company modelled parametric curves separately by treatment group. Overall survival and relapse-free survival outcomes were modelled separately for 3 groups based on data from Study 301: people in remission who had a stem cell transplant, people in remission who did not have a transplant and people who were not in remission. For people in the liposomal cytarabine–daunorubicin group who were in remission and had a stem cell transplant, the company chose a Gompertz distribution to extrapolate overall survival. This was based on clinical plausibility and because it was the best fit to the trial data. The committee considered that, although the Gompertz distribution produced a plateau, which would be expected after transplant, the plateau seemed overly optimistic. The committee agreed that the Study 301 data were not mature enough to justify this extrapolation, particularly with the amount of censoring (see [section 3.4](#)). At the first committee meeting, the committee noted that the modelled curve for the comparator group did not reach a plateau. The company stated that, after around 2 years, general population mortality rates would be applied for most people in the liposomal cytarabine–daunorubicin group in its base-case model because these rates were used when the modelled mortality rates would otherwise be lower. The ERG explored several parametric curves for extrapolating overall survival after transplant for the liposomal cytarabine–daunorubicin group. It noted that the choice of curve had a large effect on the predicted benefit and therefore the cost-effectiveness results. So, the ERG used a model averaging approach to address the uncertainty. The committee considered that this approach

did not address the clinical implausibility of the extrapolation. The committee stated that it would prefer to see a cure model for the whole population, whether or not they had a stem cell transplant. The committee agreed that a plateau, or 'cure', should be accounted for in the standard cytarabine and daunorubicin survival extrapolation (see section 3.4). It also agreed that it would prefer to see overall survival analysis based on a more mature data cut (see section 3.4) to make the long-term extrapolation more reliable. In response to consultation, the company presented statistical cure model extrapolations for the whole population. However, the company did not use these models in the cost-effectiveness results because it stated that the cure model for the whole liposomal cytarabine–daunorubicin group overestimated survival compared with the Kaplan–Meier data and gave overly favourable cost-effectiveness results. Instead, the company used cure models for overall survival after stem cell transplant, which it stated matched the updated Kaplan–Meier data well. The cure models were based on the original trial data (December 2015 data cut) because the company only had a limited dataset of updated individual patient level data, which did not include event-free status. The committee agreed that it would have preferred to have seen the whole population modelled together. The company manually set a cure fraction of 20% in the standard cytarabine and daunorubicin group. The ERG noted that this figure seemed to have been taken from a visual inspection of the Kaplan–Meier curve and that a 25% cure fraction could also be considered as a plausible upper limit. The company presented a scenario analysis that included a 25% cure fraction in the standard cytarabine and daunorubicin group. This reduced the cost effectiveness of liposomal cytarabine–daunorubicin compared with standard cytarabine and daunorubicin. The committee concluded that the model was appropriate for decision making. However, it agreed that there was still uncertainty in the difference in overall survival between the 2 treatment groups after stem cell transplant and in the cure fraction assumed for the standard cytarabine and daunorubicin group.

Event-free survival analysis for patients who had a complete response is unreliable because of small patient numbers

3.7 The company and ERG agreed that the analysis used to model event-free survival after transplant for patients who had a complete response in the

model was uncertain because of small patient numbers. The ERG also suggested that it lacked face validity. This was because there was little difference between the 2 treatment groups, unlike for overall survival after transplant. Therefore the ERG excluded these data from the model and used the overall survival analysis to inform a 2-state model. In this model, patients were either in remission or dead. This change increased the cost effectiveness of liposomal cytarabine–daunorubicin. In response to consultation, the company adopted the ERG's approach to modelling event-free survival. The committee would have preferred the whole population to be modelled together (whether or not they had a stem cell transplant) but concluded that the company's approach was appropriate for decision making.

Mortality after transplant in the economic model

Mortality rates are higher after stem cell transplant than in the general population and should be included in the model

3.8 In its base-case economic model, the company applied general population mortality rates when the modelled mortality rates would otherwise have been lower. In a scenario analysis, the company increased mortality rates after stem cell transplant compared with the general population mortality rates by applying a standardised mortality ratio of 2.34. This reduced the cost effectiveness of liposomal cytarabine–daunorubicin. The ERG considered that this scenario had face validity and therefore included it in its preferred analysis. The clinical experts stated that it was generally accepted that survival would be shorter for people who had a stem cell transplant than for the general population. The committee concluded that it was appropriate to increase the mortality rate after stem cell transplant in the model to higher than that of the general population.

Utility values in the economic model

The utility values do not have a big effect on the cost-effectiveness results

3.9 Because health-related quality-of-life data were not collected in Study 301, the company used a time-trade-off study to derive utility values for the economic model. The treatment-related disutilities included in the model were based on descriptions of the side effects of treatment provided by clinicians for the time-trade-off study. These described a more favourable side-effect profile for liposomal cytarabine–daunorubicin than for standard cytarabine and daunorubicin. Therefore a smaller disutility was applied to the liposomal cytarabine–daunorubicin group than the standard cytarabine and daunorubicin group. The ERG highlighted that this did not reflect the data from Study 301. Therefore it estimated the mean utility value for each treatment phase and applied this to both treatment groups. The ERG also noted that the utility value used by the company for the remission after transplant health state was higher than usually reported for the general population. The company also did a scenario analysis using utility values from a study by Hensen et al. (2017). In this scenario, the utility value for the remission after transplant health state was 0.75, and the ERG used this value in its preferred analysis. The ERG also adjusted the utility values for age. The committee noted that these changes did not have a big effect on the cost-effectiveness results. It concluded that it was plausible to assume the disutilities were the same in both treatment groups, to use a utility value of 0.75 for the remission health state and to adjust the utility values for age.

Costs and resource use in the economic model

Costs and resource use in the economic model do not have a big effect on the cost-effectiveness results

3.10 The company calculated treatment doses and vial use including wastage, based on a mean body surface area of 1.79 m², calculated from a UK

study of adults with cancer (Sacco et al. 2010). The ERG used a different method to calculate vial use. It accounted for the distribution of body surface area in the population, and also calculated a mean body surface area of 1.83 m² by applying the gender weighting from Study 301 to the data from the Sacco study. The ERG considered that hospital length of stay was overestimated in the model compared with that seen in Study 301. Therefore in its preferred analysis, it reduced the number of hospital days in the consolidation period. The ERG used a lower cost of stem cell transplant than the company, based on using the costs of transplants from sibling donors instead of from unrelated adult donors. It also increased the follow-up cost to reflect a 2-year follow-up, instead of 6 months. The clinical experts stated that, although sibling donors had been more common, it was now more likely that unrelated adult stem cells would be used for transplants. The committee noted that these changes to costs and resource use in the model had little effect on the cost-effectiveness results. It concluded that it was reasonable to use the ERG's method of calculating vial use, for the length of hospital stay in the model to match that in the trial and to include transplant follow-up costs for 2 years. However, it agreed that stem cells for transplant would likely come from unrelated matched donors.

Cost-effectiveness results

The most plausible incremental cost-effectiveness ratio compared with standard cytarabine and daunorubicin is lower than £50,000 per quality-adjusted life year gained

3.11 The company updated its economic model after consultation. This included the committee's preferred assumptions, specifically:

- correcting some errors identified by the ERG
- basing outcomes after transplant only on overall survival (see [section 3.7](#))
- adjusting mortality rates after transplant (see [section 3.8](#))
- using some alternative utility values (see [section 3.9](#))

- using a different method to calculate vial use (see [section 3.10](#))
- reducing the number of hospital days in the consolidation period (see [section 3.10](#)).

The company used cure models after stem cell transplant (see [section 3.6](#)) and also increased the discount in the commercial arrangement. This resulted in an incremental cost-effectiveness ratio (ICER) for liposomal cytarabine–daunorubicin of £45,055 per quality-adjusted life year (QALY) gained. When the company used a 25% cure fraction for the standard cytarabine and daunorubicin group (see [section 3.6](#)), the ICER increased to £48,127 per QALY gained. When the ERG reproduced the analyses to include the confidential commercial arrangement discount for azacitidine (included in the model as a subsequent treatment), both ICERs were below £50,000 per QALY gained. The committee concluded that the most plausible ICER was lower than £50,000 per QALY gained.

Innovation

The benefits of liposomal cytarabine–daunorubicin are captured in the cost-effectiveness analysis

3.12 The company considered that liposomal cytarabine–daunorubicin was an innovative treatment because of its formulation. The drug accumulates in the bone marrow and is released inside the cells. The company also highlighted that infusion time is reduced and that people can have it as outpatients. It also noted that liposomal cytarabine–daunorubicin is the only new treatment in recent years to show a survival benefit for people with high-risk acute myeloid leukaemia. Patient and professional groups highlighted that liposomal cytarabine–daunorubicin is the first example of this type of technology in acute myeloid leukaemia, and that it is more targeted than standard chemotherapy. The committee concluded that liposomal cytarabine–daunorubicin 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.

End of life

Liposomal cytarabine–daunorubicin qualifies as a life-extending treatment for people with a short life expectancy

3.13 The committee considered the advice about life-extending treatments for people with a short life expectancy in [NICE's guide to the methods of technology appraisal](#). It noted that the median overall survival reported in Study 301 for the comparator group was 5.95 months. It also noted that the mean modelled survival was less than 24 months in the company's model. Therefore the short life expectancy criterion of less than 24 months was met. In Study 301, overall survival in the liposomal cytarabine–daunorubicin group was higher than in the standard cytarabine and daunorubicin group by a median of 3.61 months. The mean increase in overall survival predicted by the company's model was over 2 years (undiscounted life years). Even when the ERG's least optimistic estimate of overall survival after transplant for liposomal cytarabine–daunorubicin was modelled, the mean increase in overall survival predicted by the model was more than 3 months. Therefore liposomal cytarabine–daunorubicin met the criterion of extension to life of at least an additional 3 months. The committee concluded that liposomal cytarabine–daunorubicin met NICE's criteria for being considered a life-extending treatment at the end of life.

Equalities

There are no equality issues relevant to the recommendations

3.14 Stakeholders highlighted that liposomal cytarabine–daunorubicin was more likely to be used for younger people than for older people. Because the recommendation for liposomal cytarabine–daunorubicin is for the whole population covered by the marketing authorisation, the committee concluded that its recommendations do not have a different effect on people protected by the equality legislation than on the wider population. It concluded that there are no relevant equality issues.

Conclusion

Liposomal cytarabine–daunorubicin is recommended for routine NHS use

- 3.15 The committee concluded that, with the discount agreed in the commercial arrangement, the ICERs were within the range that NICE usually considers an acceptable use of NHS resources for a life-extending treatment at the end of life. The committee recommended liposomal cytarabine–daunorubicin within its marketing authorisation for treating newly diagnosed, therapy-related acute myeloid leukaemia and acute myeloid leukaemia with myelodysplasia-related changes.

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 document.
- 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 newly diagnosed, therapy-related acute myeloid leukaemia or acute myeloid leukaemia with myelodysplasia-related changes and the doctor responsible for their care thinks that liposomal cytarabine–daunorubicin 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.

Kirsty Pitt

Technical Lead

Alexandra Filby

Technical Adviser

Gemma Barnacle

Project Manager

ISBN: 978-1-4731-3207-8