NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Liposomal cytarabine and daunorubicin for untreated acute myeloid leukaemia

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using liposomal cytarabine and daunorubicin in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using liposomal cytarabine and daunorubicin in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 14 September 2018

Second appraisal committee meeting: 27 September 2018

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Liposomal cytarabine and daunorubicin is not recommended, within its anticipated marketing authorisation, for treating newly diagnosed, therapy-related acute myeloid leukaemia or acute myeloid leukaemia with myelodysplasia-related changes in adults.

1.2 This recommendation is not intended to affect treatment with liposomal cytarabine and daunorubicin that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

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 and daunorubicin live longer than people having standard chemotherapy.

The cost-effectiveness estimates for liposomal cytarabine and daunorubicin compared with standard cytaraine and daunorubicin are variable. This is mainly because of how long-term survival was estimated and included in the economic model.

Liposomal cytarabine and daunorubicin meets NICE's criteria for being a life-extending treatment at the end of life. However, the most likely cost-effectiveness estimates are above the range that NICE normally considers acceptable. Therefore, liposomal cytarabine and daunorubicin is not recommended.

2 Information about liposomal cytarabine and daunorubicin

Anticipated marketing authorisation indication	Liposomal cytarabine and 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). On 28 June 2018 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product liposomal cytarabine and daunorubicin, intended for the treatment of acute myeloid leukaemia.
Dosage in the marketing authorisation	The company's submission states that liposomal cytarabine and 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/m^2 and cytarabine 100 mg/m^2 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/m^2 and cytarabine 65 mg/m^2 on days 1 and 3. A subsequent course of consolidation may be given when there is no disease progression or unacceptable toxicity.
Price	The price was submitted as commercial in confidence because it has not been confirmed by the Department of Health and Social Care. The company has a commercial arrangement, which would apply if the technology had been recommended.

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 therapy-related acute myeloid leukaemia or acute myeloid leukaemia 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

Treatment for therapy-related acute myeloid leukaemia and acute myeloid leukaemia with myelodysplasia-related changes 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 and second induction course, and 1 or 2 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 and 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, the results of the genetic test may not be available for 7 to 10 days. The clinical experts advised that it is becoming more common for clinicians to wait for the results of the genetic test before starting treatment. A small number of patients who have more aggressive disease would need treatment to be started more urgently. The committee agreed that no change in practice would be needed for most people who would be eligible for liposomal cytarabine and 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 and 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 and 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 North America, the baseline characteristics of people in the trial were representative of people in the UK who would be eligible for liposomal cytarabine and daunorubicin. The clinical experts explained that about a quarter of patients who would be eligible for treatment in England would be under 60 years of age. There is no biological reason to expect the benefit of treatment to be any different than the benefit 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 and daunorubicin improves overall survival but the additional benefit after stem cell transplant lacks clinical plausibility

3.4 The primary outcome measure in Study 301 was overall survival. Treatment with liposomal cytarabine and 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 and 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 and daunorubicin group (HR 0.46; 95% CI 0.24 to 0.89, p=0.0046). The committee noted that the Kaplan–Meier analysis showed a plateau in the liposomal cytarabine and daunorubicin group at around 6 months after transplant, but did not show a plateau in the standard cytarabine and daunorubicin group. The clinical experts stated that response to transplant may differ depending on someone's state of 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. The committee concluded that liposomal cytarabine and daunorubicin improved overall survival in the whole population compared to standard cytarabine and daunorubicin, but that the additional benefit after stem cell transplant, particularly in the long term lacked clinical plausibility.

Adverse effects

Liposomal cytarabine and 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 and daunorubicin had been more tolerable for them than other treatments. The clinical experts suggested that people in the liposomal cytarabine and 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 and daunorubicin group as they may have expected. The committee concluded that liposomal cytarabine and daunorubicin was generally well tolerated.

The company's economic model

There are multiple uncertainties in extrapolating post-transplant overall survival for people who had a complete response in the liposomal cytarabine and daunorubicin group

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 horizon because patients in the model were aged 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 and 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 data from Study 301 was not mature enough to justify this extrapolation, particularly with the amount of censoring (see section 3.4). 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 to most people in the liposomal cytarabine and daunorubicin group in its base-case model, because general population mortality rates were used when the modelled mortality rates would otherwise be lower. The ERG explored several parametric curves for extrapolating post-transplant overall survival for the liposomal cytarabine and 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. In response to consultation, the committee would prefer to see a cure model for the whole population, whether or not they had 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 analysis for overall survival that was based on a more mature data cut (see section 3.4) to make the long-term extrapolation more reliable. The committee concluded that the company's model was not reliable because of the uncertainties in extrapolating post-transplant overall survival for people who had a complete response in the liposomal cytarabine and daunorubicin group.

For event-free survival, the whole population should be modelled together

3.7 The company and ERG agreed that the analysis used to model post-transplant event-free survival for patients who had 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 post-transplant overall survival. Therefore the ERG excluded this data from the model and used the overall survival analysis to inform a 2-state model. In this model, patients are either in remission or are dead. This change increased the cost effectiveness of liposomal cytarabine and daunorubicin. The committee concluded that the whole population should be modelled together (whether or not they had had a stem cell transplant, see section 3.6) to reduce the uncertainty.

Post-transplant mortality 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 where 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 and 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 poorer in people who had had a stem cell transplant compared with the general population. The committee concluded that it was appropriate to increase the mortality rate after stem cell transplant.

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 was 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 and daunorubicin than for standard cytarabine and daunorubicin. Therefore a smaller disutility was applied to the liposomal cytarabine and 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 for each treatment phase and applied this utility value to both treatment groups. The ERG also noted that the utility value used by the company for the post-transplant remission health state was higher than

usually reported for the general population. The company also did a scenario analyses using utility values from a study by Hensen et al. (2017). In this scenario, the utility value for the post-transplant remission health state was 0.75, and the ERG used this value in its preferred analysis. The ERG also adjusted the utility values for ageing. 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 post-transplant remission health state, and to adjust utility values for ageing.

Costs and resource use in the economic model

The 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 1.79m^2, calculated from a UK study of adult cancer patients (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 1.83m^2 by applying the gender weighting from Study 301 to the data from the study by Sacco. The ERG considered that hospital length of stay was overestimated in the model, compared with what was 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 providing transplants from sibling donors instead of 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 in the past, recently it was 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 ICER for liposomal cytarabine and daunorubicin compared with standard cytarabine and daunorubicin is likely to be higher than £50,000 per QALY gained

3.11 The company's deterministic base case showed that the incremental cost-effectiveness ratio (ICER) for liposomal cytarabine and daunorubicin compared with standard cytarabine and daunorubicin was over £50,000 per quality-adjusted life year (QALY) gained. The exact ICER is commercial in confidence and cannot be reported here. When the confidential patient access scheme discount was included for liposomal cytarabine and daunorubicin, the ICER reduced to £46,631 per QALY gained. The ERG made some changes to the company's model in its preferred base case, including:

- correcting some errors
- including the confidential patient access scheme discount for azacitidine, included in the model as a subsequent treatment
- basing post-transplant outcomes only on overall survival (see section 3.7)
- basing post-transplant overall survival on a model averaging approach (see section 3.6)
- adjusting post-transplant mortality rates (see section 3.8)
- using some alternative utility values (see section 3.9)
- using a different method to calculate vial use (see section 3.11)
- reducing the number of hospital days in consolidation (see section 3.11)
- using a different cost of stem cell transplant (see section 3.11).

These changes resulted in an exploratory ICER that was above £50,000 per QALY gained. The committee considered that the ICER would be even higher if its preferred assumptions and model structure (a cure model with a survival plateau captured in both groups, see section 3.11) were used.

Liposomal cytarabine and daunorubicin is not recommended for routine use in the NHS

3.12 The committee agreed that it would prefer to see a cure model for the full population based on overall survival data from a more recent data cut of the Study 301 trial. The survival extrapolation should take into account a plateau in both the liposomal and standard cytarabine and daunorubicin arms. This would reduce its uncertainty in the cost-effectiveness estimates. Based on the analyses it had seen, the committee concluded that the most plausible ICER for liposomal cytarabine and daunorubicin compared with standard cytarabine and daunorubicin was likely to be higher than £50,000 per QALY gained. This was higher than the range normally considered a cost-effective use of NHS resources. Therefore it did not recommend liposomal cytarabine and daunorubicin for treating newly diagnosed, therapy-related acute myeloid leukaemia or acute myeloid leukaemia with myelodysplasia-related changes.

Innovation

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

3.13 The company considered that liposomal cytarabine and 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 it can be given as an outpatient. It also noted that liposomal cytarabine and 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 and 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 and 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 and daunorubicin qualifies as a life-extending treatment for people with a short life expectancy

3.14 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. 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 and 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 post-transplant overall survival for liposomal cytarabine and daunorubicin was modelled, the mean increase in overall survival predicted by the model was more than 3 months. Therefore, liposomal cytarabine and daunorubicin met the criterion of extension to life of at least an additional 3 months. The committee concluded that liposomal cytarabine and daunorubicin met NICE's criteria for being considered a life-extending treatment at the end of life.

Cancer Drugs Fund

Liposomal cytarabine and daunorubicin is not suitable for the Cancer Drugs Fund

3.15 Having concluded that liposomal cytarabine and daunorubicin could not be recommended for routine use, the committee then considered if it could be recommended for treating high-risk acute myeloid leukaemia within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the addendum to the NICE process and methods guides. The committee noted that the company did not make a case for liposomal cytarabine and daunorubicin to be included in the Cancer Drugs Fund. It also considered that it was likely that the most plausible ICER was higher than the range normally considered to be a cost-effective use of NHS resources. The committee agreed that liposomal cytarabine and daunorubicin did not have plausible potential to satisfy the criteria for routine use. It concluded that liposomal cytarabine and daunorubicin did not meet the criteria to be included in the Cancer Drugs Fund.

Equality considerations

There are no equality issues relevant to the recommendations

3.16 Stakeholders highlighted that liposomal cytarabine and daunorubicin would more likely be used for younger people than older people. Because the recommendation for liposomal cytarabine and daunorubicin is for the whole population in the anticipated 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.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Stephen O'Brien
Chair, Appraisal Committee
August 2018

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
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ISBN: [to be added at publication]