Cost-effectiveness of Vyxeos Liposomal® (liposomal daunorubicin and cytarabine) for the treatment of adults with newly diagnosed treatment related acute myeloid leukaemia or acute myeloid leukaemia with myelodysplasia-related changes.

The NCPE has issued a recommendation regarding the cost effectiveness of Vyxeos Liposomal® (liposomal daunorubicin and cytarabine). Following assessment of the Applicant's submission, the NCPE recommends that liposomal daunorubicin and cytarabine not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the Applicant's (Jazz Pharmaceuticals) economic dossier on the cost effectiveness of liposomal daunorubicin and cytarabine. The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified. Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision. The final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

National Centre for Pharmacoeconomics **April 2020**

Summary

In May 2019, Jazz Pharmaceuticals submitted a dossier of clinical, safety and economic evidence to support the reimbursement of Vyxeos Liposomal® (liposomal daunorubicin and cytarabine (lipo-DC)) for the treatment of adults with newly diagnosed treatment-related acute myeloid leukaemia (t-AML) or acute myeloid leukaemia with myelodysplasia-related changes (AML-MRC). Vyxeos Liposomal® is for use in the hospital-setting only.

Lipo-DC is a liposomal formulation of a fixed combination of daunorubicin and cytarabine. Each vial contains 44mg daunorubicin and 100mg cytarabine. Lipo-DC has a different posology and must not be interchanged with other daunorubicin and /or cytarabine containing products. Daunorubicin has anti-mitotic and cytotoxic activity, inhibiting topoisomerase II, DNA polymerase, and producing DNA-damaging free-radicals. Cytarabine is a cell cycle phase-specific antineoplastic agent, working during the S-phase of cell division. Intracellularly, cytarabine is converted into ara-CTP, the active metabolite, which works primarily through inhibition of DNA synthesis.

For the first induction course: lipo-DC is administered, via intravenous infusion, at a dose of daunorubicin 44mg/m^2 and cytarabine 100mg/m^2 on days 1, 3 and 5. If a second induction course is required (dependent on patient response) the dose is daunorubicin 44mg/m^2 and cytarabine 100mg/m^2 on days 1 and 3. A maximum of two consolidation courses can be administered if required (dependent on patient response) at a dose of daunorubicin 29mg/m^2 and cytarabine 65mg/m^2, on days 1 and 3.

The primary comparator is daunorubicin and cytarabine administered as separate intravenous infusions (in a non-liposomal formulation) according to the daunorubicin and cytarabine 3+10 regimen. A second induction course, if required (dependent on patient response), can be administered according to the daunorubicin and cytarabine 3+8 regimen (see
Table 1). Options for consolidation therapy if required (dependent on patient response) include regimens containing cytarabine with or without daunorubicin. This is the current standard of care in Ireland.

Table 1 Comparator treatment regimen

First induction course		
daunorubicin and cytarabine 3+10	Daunorubicin	60mg/m^2 IV bolus on days 1,3 and 5
	Cytarabine	100mg/m^2 IV infusion over 30 minutes twice daily for days 1 to 10 inclusive.
Second induction course		
daunorubicin and cytarabine 3+8	Daunorubicin	50mg/m^2 IV bolus on days 1,3 and 5
	Cytarabine	100mg/m^2 IV infusion over 30 minutes twice daily for days 1 to 8 inclusive.

IV: intravenous

1. Comparative effectiveness of liposomal daunorubicin and cytarabine

Clinical evidence for the approval of lipo-DC comes from the CLTR0310-301 trial (a phase III, open-label, multi-centre randomised controlled trial), in addition to two phase II trials. The CLTR0310-301 trial compared lipo-DC to the daunorubicin and cytarabine 3+7 regimen for induction and second induction and consolidation courses using daunorubicin and cytarabine 2+5 regimen (Table 2). Eligible patients (ECOG performance score 0-2) were aged 60 to 75 years at the time of diagnosis of t-AML, AML-MRC, or de novo AML with cytogenetic characteristics of myelodysplastic syndromes. The primary endpoint was overall survival (OS). Patients were randomised 1:1; 153 to the lipo-DC arm and 156 to the daunorubicin and cytarabine 3+7 arm. Patients could receive up to two induction courses and two consolidation courses in both arms (according to response). Patients with documented response were eligible for consolidation courses. Baseline characteristics were similar between arms. More patients in the lipo-DC arm had favourable and intermediate risk cytogenetics, and fewer were of ECOG performance status 2. The median duration of follow-up was approximately 20 months in both arms. Efficacy analyses are presented in the intention-to-treat population.

Table 2 Dosage regimens administered in the CLTR0310-301 trial

Arm 1: Lipo-DC (N=153)	Arm 2: daunorubicin and cytarabine 3+7 (N=156)
First Induction Course	
Daunorubicin 44mg/m^2 and cytarabine 100mg/m^2 IV infusion, days 1,3 and 5	Daunorubicin 60mg/m^2 IV infusion, days 1, 2, 3 Cytarabine 100mg/m^2 IV continuous infusion, days 1 to 7 inclusive
Second Induction Course	
Daunorubicin 44mg/m^2 and cytarabine 100mg/m^2 IV infusion, days 1 and 3	Daunorubicin 60mg/m^2 IV infusion, days 1 and 2. Cytarabine 100mg/m^2 IV continuous infusion, days 1 to 5 inclusive
Consolidation therapy (up to 2 courses)	
Daunorubicin 29mg/m^2 and cytarabine 65mg/m^2 IV infusion on days 1 and 3	Daunorubicin 60mg/m^2 IV infusion, days 1 and 2. Cytarabine 100mg/m^2 IV continuous infusion, days 1 to 5 inclusive

IV: intravenous

Lipo-DC was associated with an increase in OS, HR 0.69 (95% CI 0.52 to 0.90; p=0.005). Median OS with lipo-DC was 9.56 months (95% CI 6.6 to 11.86) vs. 5.95 months (95% CI 4.99 to 7.75). When OS was censored at haematopoietic stem cell transplant (HSCT), no statistically significant difference was seen between arms (HR 0.81, 95% CI 0.6 to 1.09; p=0.165). Thus, some of the treatment benefit observed for lipo-DC may be attributable to HSCT. Complete remission was achieved in 37.3% and 25.6% (p=0.04) of the respective arms. Complete remission or complete remission with incomplete blood count recovery was achieved in 47.7% vs. 33.3%, (p=0.016). There was no statistically significant difference in median remission duration, 6.93 months vs. 6.11 months, HR 0.77 (95% CI 0.47 to 1.26; p=0.291). Overall, 34% and 25% of patients in the respective arms received a HSCT.

For the cost-effectiveness evaluation, equal efficacy was assumed for the daunorubicin and cytarabine 3+10 and the daunorubicin and cytarabine 3+7 regimens. No evidence synthesis was undertaken. There is some uncertainty as to whether these regimens are clinically comparable.

CLTR0310-301 trial has limited generalizability. Eligible patients were aged 60 to 75 years at the time of diagnosis of AML. The dosage regimens for the comparators were not in line with clinical practice in Ireland. There were differences in the post-protocol patient management (including eligibility for HSCT). Further, clinical opinion indicates that the outcomes seen in the control arm were poorer than would be expected in Irish clinical practice.

2. Safety of liposomal daunorubicin and cytarabine

In CLTR0310-301, all patients experienced at least one treatment emergent adverse event (TEAE). Grade ≥3 TEAEs occurred in about 92% of both arms; the most common with lipo-DC were febrile neutropenia (68%), pneumonia (20%), hypoxia (13%), hypertension and bacteraemia (10%) and sepsis (9%). The most common grade ≥3 TEAEs with daunorubicin and cytarabine 3+7 were febrile neutropenia (71%), pneumonia and hypoxia (15%), sepsis and respiratory failure (7%) and fatigue (6%). Almost all patients in both arms experienced at least one infection-related adverse event. Bleeding events ≥ grade 3 occurred in 11.8% and 8.6% of patients in the respective arms. Four patients in each arm died due to a

bleeding-related adverse event. Cardiac events of grade ≥3 occurred in 15.7% and 17.9% of patients in the respective arms. Median time to recovery from neutropenia was 44 days vs. 35 days and from thrombocytopenia was 49 days vs. 44 days. All-cause mortality (within 100 days post-HSCT) occurred in 9.6% vs. 20.5% of the respective arms. Mortality in patients with refractory AML occurred in 3.8% vs. 7.7% of the respective arms.

3. Cost effectiveness of liposomal daunorubicin and cytarabine

Cost-effectiveness was investigated, from the HSE perspective, using a cost-utility model with a 30 year time horizon. The model used a decision tree to allocate patients to different cohorts by response (post-induction remission or lack of remission) and HSCT outcomes, followed by partitioned survival models (for subsequent disease progression and mortality). Separate partitioned survival models are used to model outcomes and costs for: responders who do not receive HSCT, responders who receive HSCT, and non-responders. Health states included were: AML, remission, post-HSCT remission, progression, and death. The time spent in health states was derived using post-hoc responder analyses of the CLTR0301-301 trial. Treatment effects were not modelled for non-responders.

The approach to modelling HSCT is inconsistent. HSCT is included in the decision tree component for responders and in the partitioned survival component for non-responders. The Review Group consider that including HSCT as a health state in the partitioned survival component for all patients would be more appropriate. Further, post hoc analyses with exclusions of patient data by the Applicant, indicate that the modelling approach used may not be appropriate. Also, as a result of the chosen model structure, many statistical analyses, used to inform the model, were carried out on groups containing small numbers of patients. The resulting parameter estimates are likely to be unstable, increasing the uncertainty in model outputs.

A number of aspects in the modelling approach may have biased the cost-effectiveness estimates in favour of lipo-DC. Patients in the lipo-DC arm, who achieve post-induction remission (in the decision tree), enter the partitioned survival component sooner than patients in the comparator arm. Patients in the lipo-DC arm can, thus, accumulate health benefits in the partitioned survival component for longer. Also, the analyses of post-HSCT

survival, used to inform treatment effectiveness, may compound any existing biases in the trial data. The criteria for HSCT were not clearly defined and the decision to transplant was not blinded to treatment allocation.

Under an assumption of improved response in younger patents, an odds ratio of 1.9 was applied to response for patients aged less than 60 years relative to the 60 to 69 years group. However, this odds ratio was informed by a study in adults aged 60 years and older. It is uncertain; an assessment of model sensitivity to this parameter was not provided.

An annual discount rate of 4% is applied to costs and outcomes. Health outcomes were expressed in quality adjusted life years (QALYs). Health state utility values were used, with decrements for courses of induction and consolidation treatment, and HSCT. Utility values were derived from a time-trade-off study with a one year horizon in the UK general population. Utility values are uncertain. Clinical opinion suggests that there is a life-long reduction in health-related quality-of-life following HSCT, but the utility value for post-HSCT remission is higher than age-adjusted general population norm. There were also inconsistencies in the study vignettes used to inform treatment-related decrements. Costs included were: drug acquisition and administration costs, subsequent therapies, adverse events, HSCT costs and health state costs. Costs applied for treatment administration were higher for daunorubicin and cytarabine 3+10 than for lipo-DC. Given the similar administration requirements, and potentially longer hospital stay with lipo-DC (due to prolonged neutropenia), this approach lacks face validity.

Results

Under the Applicant's proposed base case the incremental cost-effectiveness ratio (ICER) is €40,212 per QALY (incremental cost €36,792/incremental QALY 0.91).

The Review Group have made a number of changes to the base case assumptions, including: inpatient treatment in line with clinical opinion, using DRG costs for inpatient stays, an increased hospital stay for lipo-DC (due to prolonged neutropenia), using a lower utility value for the post-HSCT remission health state, and applying the same utility decrements for induction treatment with lipo-DC and daunorubicin and cytarabine 3+10.

Under the Review Group adjusted base case, the ICER is €79,606 per QALY (incremental cost €63,261/incremental QALY 0.79). Probabilities of cost effectiveness are 0% (at €20,000 per QALY) and 0% (at €45,000 per QALY); the probabilistic mean ICER is €79,647 per QALY.

Deterministic sensitivity analyses indicate that this ICER is most sensitive to changes in the discount rate (for health outcomes) and health state utility values. The Applicant did not provide model functionality to fully explore uncertainty associated with survival extrapolations. Feasible scenario analyses indicate that the ICER is most sensitive to assumptions around treatment effects, some survival extrapolations and time horizon.

4. Budget impact of liposomal daunorubicin and cytarabine

The price to wholesaler per vial of lipo-DC is €5,200. The total cost per vial to the HSE (inclusive of rebate) is €4,914.00 (excl VAT) and €6,110.00 per vial (incl VAT). The mean drug cost per patient per course (€54,990 (incl VAT)) was estimated from the proportion of patients who received induction and consolidation courses in the CLTR0310-301 trial.

It was estimated that there would be 17 patients eligible for treatment in year one, and 18 patients annually thereafter. When the Applicant's market share estimates are applied, the Applicant estimate of gross budget impact was €1.43 million over five years (incl VAT). The Applicant estimate of net budget impact was €1.39 million over five years (incl VAT).

Clinical opinion to the Review Group indicates that the Applicant's market share estimates were likely conservative. Thus, the reported budget impact assessment is likely an underestimate.

5. Patient Organisation Submissions

No Patient Organisation Submissions were received in the course of this appraisal.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that Vyxeos Liposomal® (liposomal daunorubicin and cytarabine) not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments.

This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.