



Cost-effectiveness of gemtuzumab ozogamicin (Mylotarg®) (with daunorubicin & cytarabine) for the treatment of patients ≥ 15 years with previously untreated, de novo CD33-positive acute myeloid leukaemia, except acute promyelocytic leukaemia

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation. Following assessment of the applicant's submission, the NCPE recommends that gemtuzumab ozogamicin (Mylotarg®) 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. The HSE asked the NCPE to carry out an assessment of the applicant's (Pfizer Healthcare Ireland) economic dossier on the cost effectiveness of gemtuzumab ozogamicin (Mylotarg®) (with daunorubicin & 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.

Summary

In November 2018, Pfizer Healthcare Ireland made a submission on gemtuzumab ozogamicin (with daunorubicin & cytarabine) for the treatment of patients ≥ 15 years with previously untreated, de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia. Final data, required by the NCPE, was received on 17th June 2019. Gemtuzumab ozogamicin is an antibody-drug conjugate that combines a humanised, anti-CD33, monoclonal antibody with calicheamicin, a potent antitumor antibiotic that causes DNA damage.

Licensed dose

Induction: Gemtuzumab ozogamicin 3 mg/m^2 /dose (maximum of 5 mg) on days 1, 4, and 7 in combination with daunorubicin 60 mg/m^2 /day on day 1 to day 3, and cytarabine 200 mg/m^2 /day on day 1 to day 7 (i.e. the 'daunorubicin & cytarabine 3 + 7 regimen').

Gemtuzumab ozogamicin should not be administered during second induction therapy.

Consolidation (for patients experiencing a complete response following induction): Up to two consolidation courses of gemtuzumab ozogamicin 3 mg/m^2 /dose (maximum of 5 mg) on day 1 in combination with daunorubicin 60 mg/m^2 (for 1 day (first course) or 2 days (second course)) and cytarabine $1,000 \text{ mg/m}^2$ every 12 hours on day 1 to day 4.

1. Comparative effectiveness of gemtuzumab ozogamicin (with daunorubicin & cytarabine).

ALFA-0701 was an open-label, phase 3 randomised controlled trial (January 2008 to November 2010) in patients (50 - 70 years) with untreated de novo AML. Patients (n=280) were randomised 1:1 to induction with the 'daunorubicin & cytarabine 3 + 7 regimen' without (comparator arm) or with gemtuzumab ozogamicin (gemtuzumab ozogamicin arm). A second induction course, with daunorubicin & cytarabine, was given if leukaemic blast cells persisted at the day 15 bone marrow aspirate. Patients with a complete response (with/without complete platelet recovery) received up to two consolidation courses of daunorubicin & cytarabine with or without gemtuzumab ozogamicin according to randomisation. Patients with non-favourable cytogenetics could be offered allogeneic haematopoietic stem-cell transplant (HSCT). Patients who experienced remission were eligible for allogeneic HSCT.

The initial cut-off date was August 2011. Outcomes from the April 2013 cut-off date were used in the submission; median follow-up was 47.6 months (gemtuzumab ozogamicin arm) and 41.0 months (comparator arm). Study treatment was completed by 62.6% and 65.0% of patients in the respective arms. The primary endpoint was event-free survival (investigator assessment) in the modified intention-to treat population. Median event-free survival was 17.3 months vs. 9.5 months in the respective arms; hazard ratio (HR) = 0.56 (95% CI, 0.42 to 0.76); $p = 0.0002$. Probabilities of being event free at 2 years were 42.1% (95% CI, 32.9 to 51.0) vs. 18.2% (95% CI, 11.1 to 26.7) and at 3 years were 39.8% (95% CI, 30.2 to 49.3) vs. 13.6% (95% CI, 5.8 to 24.8). In a retrospective, blinded independent review committee analysis, median event-free survival was 13.6 months (gemtuzumab ozogamicin) vs. 8.5 months (comparator); HR = 0.66 (95% CI, 0.49 to 0.89); $p = 0.006$. Probabilities of being event free at 2 years were 38.5% (95% CI, 29.6 to 47.3) vs. 18.1% (95% CI, 11.1 to 26.5) and at 3 years were 36.5% (95% CI, 27.3 to 45.7) vs. 13.6% (95% CI, 5.8 to 24.7). On request from the Review Group, outcomes from the blinded independent review committee analysis were used in the base case cost-effectiveness analysis instead of those from the investigator assessment. Secondary outcome analyses revealed that the median relapse-free survival was 28.0 months (gemtuzumab ozogamicin) vs. 11.4 months (comparator); HR = 0.526; $p = 0.0006$. There were no statistical differences in the rates of complete response (70.4% vs. 69.9%) and complete response (with incomplete platelet recovery) (11.1% vs. 3.7%). Median overall survival was 27.5 months vs. 21.8 months; HR = 0.81 (95% CI, 0.60 to 1.09); 2-sided $p = 0.16$. In total 23.7% and 39.0% of the respective arms received a HSCT either in first remission or after induction failure or relapse. Censoring at time of transplant had no impact on overall survival. Health related quality of life outcomes were not measured.

The Review Group note that the trial does not provide data on the treatment of adolescent patients (15 - 17 years), or adult patients <50 years or >70 years. Cost effectiveness in these age groups is thus based on extrapolation. CD33-positive expression was not a requirement for enrolment in ALFA-0701; subgroup analyses were exploratory only. The comparator (the 'daunorubicin & cytarabine 3 + 7 regimen') is not fully reflective of potential comparators. The Health Service Executive (HSE) National Cancer Control Programme treatment protocols describe a 'daunorubicin & cytarabine 3 + 10' regimen (course 1 induction), a 'daunorubicin

& cytarabine 3 + 8' regimen (course 2 induction) and a high/ intermediate dose cytarabine monotherapy consolidation regimen.

The comparator in the base case cost-effectiveness analysis is the 'daunorubicin & cytarabine 3 + 10' regimen. The 'daunorubicin & cytarabine 3 + 7' regimen is investigated in a scenario analysis; however this makes minimal difference to the ICER. Choice of regimen only affects incremental costs and not the efficacy data input into the model. The Review Group requested that the base case was updated to also reflect costs of intermediate dose cytarabine. We note that the efficacy data input into the model remained unchanged in this update.

2. Safety of gemtuzumab ozogamicin (with daunorubicin & cytarabine).

ALFA-0701 safety analyses were based on patients (n=268) who received at least one dose of study treatment. Safety data presented in this submission was derived from two analyses of ALFA-0701 data; a prospective assessment of predefined Grade 3- 4 treatment-emergent adverse events and a retrospective assessment of treatment-emergent adverse events of special interest. This approach may underestimate the impact of adverse events on costs and disutilities.

The all grade treatment-emergent adverse events that occurred $\geq 5\%$ of either arm were haemorrhage (90.1% (gemtuzumab ozogamicin) vs. 78.1% (comparator)), mucosal toxicity (16.1% vs. 6.6%), pain (14.5% vs. 3.6%), the composite (nausea, vomiting, and diarrhoea) (16.8% vs. 10.2%), skin toxicity (16.8% vs. 10.7%), pulmonary toxicity (13.9% vs. 13.0%) and central nervous system toxicity (6.1% vs. 2.9%). Veno-occlusive disease occurred in 4.6% vs. 1.5%. Treatment-emergent adverse events that led to permanent discontinuation occurred in 31.1% vs. 7.3% of the respective arms. Serious adverse events were reported in 67.2% vs. 55.5 % of the respective arms. The most commonly reported treatment-emergent serious adverse events were infections (41.2% vs. 38.0%). At the April 2013 cut-off, 62.0% of study patients had died (59.3% vs. 64.7% of the respective arms).

3. Cost effectiveness of gemtuzumab ozogamicin (with daunorubicin & cytarabine).

The perspective of the evaluation was that of the HSE. Patients enter the lifetime cohort state-transition model and receive one or two induction courses. Those who attain complete response (with/without incomplete platelet recovery) may receive up to two consolidation courses. In alignment with ALFA-0701 data, a proportion of patients do not complete consolidation and a proportion receive a HSCT. Patients in complete response (with/without complete platelet recovery) who relapse, and those who are refractory to induction, move to second-line therapies. The proportion of patients who are fit enough for salvage therapy is based on limited clinical opinion. A proportion of patients who receive salvage therapy subsequently receive a HSCT. A proportion of patients who attain second-line complete response (with/without complete platelet recovery) will not receive a HSCT, but will have prolonged survival. Patients who remain in complete response for 5 years move to the long-term functionally cured state. On request, the hazard ratio for the long-term survivors (after five years) versus the general population was recalculated to assume that patients with AML had at least the same probability of death each year as the general population. Survival functions were fitted to the ALFA-0701 Kaplan-Meier data to model:

- Relapse-free survival (for patients in complete response with/without complete platelet recovery).
- Overall survival for patients in complete response with/without complete platelet recovery (herein 'OS-remission').
- Overall survival for the refractory patients (herein 'OS-refractory')

The applicant explored standard parametric models, mixture cure models (MCM), and flexible spline models. The MCM Log-Normal curve was the best fitting curve for relapse-free survival. For OS-remission, the applicant chose the MCM Weibull curve and the MCM Log-Normal curve for the gemtuzumab ozogamicin and comparator arms respectively. The differences between the fit of the MCM Weibull and MCM Log-normal models for both treatment arms were small. As such, the Review Group updated the model to fit the MCM Weibull curve for both arms. The Gompertz parametric curve was the best fit for OS-refractory. The probabilities of undergoing HSCT from the various health states were calculated from ALFA-0701 time-to-HSCT analyses. In the original submission, these were pooled across treatment arms for the complete response and refractory states whilst data from individual arms was used for the relapse state. The Review Group updated the model to use data from pooled arms for all states (in line with clinical opinion and for consistency).

The model includes two health states for post-HSCT (i.e. with and without graft versus host disease). In both, it is assumed that all patients achieve complete response (with/without complete platelet recovery) after HSCT. The Review Group do not consider this to be a reasonable assumption. We requested that the model account for relapse after HSCT in a proportion of patients. The applicant declined to make this change.

In general, the utility values used in the model are highly uncertain; a number of unfounded assumptions are made. For the base case, a number of utility values were derived from NICE TA399 (Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts - 2016). These were applied to a range of disparate health states. For the long-term functionally cured health state, the applicant assumes a baseline of perfect health. The model includes disutilities associated with Grade 3-4 treatment-emergent adverse events of special interest (that occurred in $\geq 1\%$ of both arms) and infections, cardiac disorders and veno-occlusive disease. The model includes drug acquisition costs, health state costs and costs associated with adverse events, HSCT and terminal care. In general, the costs in the model are also highly uncertain. On request, a number of changes to the costs were made including changes to the costs of comparator regimens (to include cytarabine monotherapy consolidation), changes to the salvage regimens and supportive therapies, changes to the cost of HSCT, and the application of a number of Irish derived costs.

Results

In the original applicant base case, the incremental cost-effectiveness ratio (ICER) was €14,534/QALY (Incremental Costs: €12,901, Incremental QALYs: 0.89). In the course of the NCPE evaluation, a number of changes were made to the model. These included the use of the ALFA-0701 blinded independent review committee data, changes to the long-term survival hazard ratio, use of alternative survival curves, use of pooled HSCT data, changes to the proportion of patients who receive salvage, and changes to some cost, resource and utility data. The resultant NCPE preferred base case ICER is €49,654/QALY (Incremental Costs: €29,446, Incremental QALYs: 0.59). Deterministic sensitivity analyses indicated that the model was generally insensitive to changes in input parameters. The Review Group ran scenario analyses on all plausible survival curves; resultant ICERs ranged from €32,052/QALY to €50,154/QALY. The applicant included three alternative options for utility input sources in

the model; all sources were uncertain. The resultant ICERs ranged from €42,559/QALY to €50,515/QALY. Using the NCPE preferred base case, at a willingness-to-pay threshold of €20,000/QALY, the probability of being cost-effective is 18.4%. At a threshold of €45,000/QALY, the probability is 45.7%.

4. Budget impact of gemtuzumab ozogamicin (with daunorubicin & cytarabine)

Gemtuzumab ozogamicin is supplied as a single 5mg vial (powder for concentrate for solution for infusion). The ex-factory price is €7,200 per vial. A maximum of five vials is recommended per patient. The cost per treatment course is €42,300 per patient (including VAT & rebate).

The applicant estimates that the number of patients eligible for treatment will be 76 in year 1 increasing to 81 in year 5. The applicant's chosen uptake rate was informed by assumptions regarding concurrent recruitment of patients to clinical trials. We requested that this assumption be removed in the base case analysis; the applicant declined. Instead, the Review Group removed the assumption and we assume an uptake rate of 100%. First-line treatment costs were derived from ALFA-0701 treatment consumption data. We estimate that the gross budget impact of treatment with gemtuzumab ozogamicin (with daunorubicin & cytarabine 3 + 10' regimen) will be €2.99 million in year 1, increasing to €3.18 million in year 5; 5-year cumulative impact of about €15.42 million. We estimate that the net budget impact of treatment with gemtuzumab ozogamicin (with daunorubicin & cytarabine 3 + 10' regimen) will be €2.67 million in year 1, increasing to €2.75 million in year 5; 5-year cumulative impact of about €13.43 million. With the applicant's assumed uptake rate (35% in year 1, increasing to a 60% by year 5) the estimated 5-year gross cumulative impact is €8.20 million and the estimated 5-year net cumulative impact is €7.15 million.

5. Patient submissions.

No patient organisation submissions were received during the course of this appraisal.

6. Conclusion

For this submission, direct evidence is derived from the ALFA-0701 trial. The trial does not provide data on the treatment of adolescent patients (15 - 17 years), or adult patients <50 years or >70 years. CD33-positive expression was not a requirement for enrolment in ALFA-0701. The cohort state-transition model is generally aligned with ALFA-0701 however there are a number of model structure limitations. The model assumes that patients who remain in complete response for 5 years move to the functionally cured state (and have a baseline of perfect health). In general, the utility values and cost data input into the model are highly uncertain.

Following NCPE assessment of the company submission, gemtuzumab ozogamicin (Mylotarg®) (with daunorubicin and cytarabine) is not considered cost effective for the treatment of patients ≥ 15 years with previously untreated, de novo CD33-positive acute myeloid leukaemia, except acute promyelocytic leukaemia, and therefore is not recommended for reimbursement at the submitted price.