Cost-effectiveness of inotuzumab ozogamicin (Besponsa®) for the treatment of adults with relapsed or refractory CD22 positive B-cell precursor acute lymphoblastic leukaemia (ALL).

The NCPE assessment of inotuzumab ozogamicin has demonstrated evidence of benefit in terms of remission rates, rates of haematopoietic stem cell transplant (HSCT) and overall survival (OS), although the size of the long-term OS gain is highly uncertain. There is a very low probability of cost-effectiveness and a high probability that the ICER exceeds the cost effectiveness thresholds for existing treatments. The NCPE recommend that inotuzumab should be considered for reimbursement if 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 National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Pfizer Ireland) economic dossier on the cost effectiveness of inotuzumab ozogamicin (Besponsa®). 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 (NCCP) 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.

National Centre for Pharmacoeconomics **September 2018**

Summary

In March 2018, Pfizer Ireland submitted a dossier of clinical, safety and economic evidence in support of inotuzumab for the treatment of adult patients with relapsed or refractory CD22 positive B-cell precursor acute lymphoblastic leukaemia (ALL). Final data submitted by the applicant was received in August 2018.

Inotuzumab ozogamicin is a humanised CD22 targeted antibody drug conjugate (ADC), with the cytotoxic agent calcicheamicin. After binding to CD22 on the CD22 expressing tumour cell, the ADC complex is internalised, the antibody cleaved from the drug molecule, releasing the calcicheamicin inside the cell. Calcicheamicin can induce double strand DNA breaks, inducing cell cycle arrest and apoptotic cell death. Inotuzumab is administered by IV infusion over 60 minutes, in the outpatient setting. In the first cycle, the dose is 1.8mg/m^2, given as 0.8 mg/m^2 Day 1 and 0.5 mg/m^2 Day 8 and Day 15. Cycle duration is 3 weeks but may be extended to 4 weeks if the patient achieves remission. The dose in subsequent cycles depends on response; for patients achieving remission the dose is 1.5mg/m^2 given as 0.5mg/m^2 on D1, D8 and D15. All cycles after cycle 1 are 4 weeks in duration. For patients proceeding to HSCT, treatment duration is 2 cycles or up to 3 cycles if the patient did not achieve remission or MRD negativity. For patients not proceeding to SCT, treatment duration is for a maximum of 6 cycles. In all cases, treatment should be discontinued if remission is not achieved within 3 cycles.

1. Comparative effectiveness of inotuzumab

In the submission, the chemotherapy regimen FLAG-IDA (fludarabine, idarubicin, cytarabine and filgrastim) was the comparator investigated. At the request of the NCPE, a comparison with blinatumomab was also presented.

Relative efficacy outcomes for the comparison with FLAG-IDA were derived from the INO-VATE study. This study was an open-label, multinational, phase III randomised controlled trial (RCT) of 326 patients with relapsed or refractory B precursor relapsed or refractory (R/R) ALL. Patients were assigned to treatment on a 1:1 basis, inotuzumab as per the dosage schedule outlined below (Table 1), or the Investigator's choice of one of three standard of care (SOC) treatment options (Table 1). FLAG-IDA was not included as a SOC treatment option in the INO-VATE trial. The primary end-point of the INO-VATE study was complete

remission (CR)/complete remission with incomplete haematologic recovery (CRi) in the ITT218 population i.e. the Intention-To-Treat analysis of the first 218 randomised patients.

Table 1Dosing schedule of all treatment arms in INO-VATE

Treatment	Dosing schedule
Inotuzumab	Cycle 1 dose is 1.8mg/m^2, given as 0.8 mg/m^2 Day 1 and 0.5 mg/m^2 Day 8 and Day 15 of 21-day cycle. The dose in subsequent cycles depends on response. For patients not achieving CR/CRi, dosing is as per Cycle 1. For patients achieving a CR/CRi, the dose in subsequent cycles is 1.5mg/m^2, given as 0.5mg/m^2 on Days 1, 8 and 15. All cycles after cycle 1 are 4 weeks in duration. A maximum of 6 cycles can be administered.
FLAG	Up to 4 cycles (28 days each) could be administered. Cytarabine 2g/m^2/day, days 1-6, fludarabine 30mg/m^2 days 1-5 and G-CSF 5microgram/kg per day at the institutional dose.
HiDAC	For up to one 12 dose cycle of cytarabine, at a dose of 3g/m^2 every 12 hours, or a dose of 1.5g/m^2 for patients aged ≥55 years.
Cytarabine & mitoxantrone	Up to 4 cycles (15-20 days each) could be administered. Cytarabine 200mg/m^2/day, days 1-7 Mitoxantrone 12mg/m^2/day days 1-3

The trial met its primary endpoint of an increase in CR/CRi in the ITT218, with a rate of 80.7% with inotuzumab compared to 29.4% with SOC. In the full ITT population, inotuzumab was associated with an increase in progression free survival (PFS) HR 0.45 (97.5% CI 0.34, 0.61), median PFS 5 months with inotuzumab versus 1.8 months with SOC. Inotuzumab was associated with a non-statistically significant increase in OS, HR 0.77 (97.5% CI 0.58-1.03). The EMA Rapporteur recommended using a one-sided test (0.025) for OS, which rendered the improvement with inotuzumab statistically significant. The rate of SCT was higher with inotuzumab than SOC (41% v's 11%). The applicant provided additional academic in confidence information regarding the clinical efficacy of inotuzumab which was considered by the NCPE.

Comparative efficacy with blinatumomab was derived from matched adjusted indirect comparison (MAIC) between INO-VATE and the TOWER study. The NCPE expressed concern that this method was associated with significant uncertainty and conclusions on cost-effectiveness from this comparison should be treated with caution.

2. Safety of inotuzumab

Safety and tolerability was a secondary endpoint of the INO-VATE study. AEs were reported in virtually all patients in both arms. The incidence of Grade 3-4 AEs was similar in both arms across all cycles, occurring in 89.6% of inotuzumab treated patients. Serious AEs (SAE) of any grade, and of Grade≥3 occurred in similar numbers of patients in both arms, at 48% and 46% respectively with inotuzumab. Discontinuation due to AEs occurred in 18.9% patients in the inotuzumab arm of INO-VATE. Based on the March 2016 analysis, all causality Grade 5 (death) treatment emergent AEs (TEAEs) were reported for 17 inotuzumab patients compared with 11 SOC patients. Veno-occlusive disease (VOD) was reported in 15 patients. Specific measures have been introduced in the SPC to reduce the risk of VOD e.g. limiting inotuzumab treatment to 3 cycles for those expected to receive HSCT, avoiding dual alkylating conditioning regimens for HSCT, monitoring of liver function tests while on treatment etc. The applicant provided additional updated safety information which was considered by the NCPE.

3. Cost effectiveness of inotuzumab

For the cost-effectiveness analysis, the key effectiveness inputs in the model were OS, PFS CR/CRi, and rate of HSCT, derived from the INO-VATE study, and for the comparison with blinatumomab, from the MAIC. Cost-effectiveness was investigated using a five health state model, with a 60-year time horizon. The model simulates patients through five health states: 'Stable', 'CR/CRi', 'Post-HSCT', 'Progressed Disease' and 'Death'. Transitions from Stable to CR/CRi and Post-HSCT are based on CR/CRi and HSCT rates from INO-VATE, while time spent within these states or progressing to the 'Progressed Disease' and 'Death' states is driven by the PFS and OS curves. All health states are mutually exclusive, and 'Death' is the absorbing state. Patient characteristics, dose intensity, and utility measurements used in the model are derived from INO-VATE. The NCPE have concerns regarding the use of the FLAG-subgroup of the INO-VATE SOC arm as a surrogate for FLAG-IDA, as it is likely to underestimate the efficacy of SOC treatment. The NCPE note that the applicant provided two additional scenario analyses using alternative inputs for FLAG-IDA efficacy, which did not demonstrate a significant impact on the ICER.

Survival outcomes from INO-VATE were extrapolated to the full-time horizon of the model, using a variety of extrapolation methods. Resource use in the model captured costs for drug acquisition and administration, costs of SCT, salvage therapy and terminal care.

The incremental cost per QALY (incremental cost-effectiveness ratio (ICER)) in the applicant's base case was €68,920/QALY (incremental costs €92,755, incremental QALYs 1.346). The probability of cost-effectiveness at a threshold of €20,000/QALY was 0%, and at a threshold of €45,000/QALY was 2.8%.

The NCPE implemented a number of changes to the model based on plausible alternative assumptions. The NCPE consider that it is likely the ICER falls within a range of €52,183/QALY (incremental costs €63,962, incremental QALYs 1.226) to €84,983/QALY (incremental costs €104,166, incremental QALYs 1.226). The probability of cost-effectiveness at a threshold of €20,000/QALY was 0% to 0.2%, and at a threshold of €45,000/QALY was 0.1% to 25%, depending on model assumptions.

4. Budget impact of inotuzumab

Inotuzumab is submitted for reimbursement under the hospital oncology drugs management system. The proposed ex-manufacturer price per 1mg vial is €9,970. The reimbursement cost for a treatment course of three cycles (10 vials) for a patient is €94,217 ex VAT and €117,148 including VAT. Based on the applicant estimate of the eligible population and assuming 100% market share, the projected gross budget impact of the drug acquisition over the first five years is €5.815 million including VAT. The net budget impact is €5.554 million including VAT. These estimates are highly sensitive to treatment duration and are based on the assumption of only three cycles per eligible patient. The use of inotuzumab will likely be associated with cost offsets through reduced hospitalisation which are not included in the above estimates.

5. State if any patient submissions were received, and name submitting organisations.

No patient organisation submissions were received during this HTA.

6. Conclusion

The NCPE assessment of inotuzumab has demonstrated additional benefit in terms of increased remission rates, increased rates of HSCT and a statistically significant improvement in OS, but the magnitude of this benefit in the long-term is uncertain. There is a low probability of cost-effectiveness and a high probability that the ICER exceeds the cost-

effectiveness threshold for existing treatments. The NCPE recommends that inotuzumab should be considered for reimbursement if 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.