inotuzumab ozogamicin 1mg powder for concentrate for solution for infusion (BESPONSA®)  
SMC No 1328/18
Pfizer Ltd

4 May 2018

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission assessed under the ultra-orphan and end of life medicine process

**inotuzumab ozogamicin (BESPONSA®)** is accepted for restricted use within NHS Scotland.

**Indication under review:** as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL). Adult patients with Philadelphia chromosome positive relapsed or refractory B cell precursor ALL should have failed treatment with at least one tyrosine kinase inhibitor.

**SMC restriction:** in patients for whom the intent is to proceed to stem cell transplantation.

A phase III open label randomised controlled study demonstrated improvements in remission rates and overall survival for the patient population under review when treated with inotuzumab ozogamicin compared with standard chemotherapy.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of inotuzumab ozogamicin. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Published 11 June 2018
**Indication**

As monotherapy for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL). Adult patients with Philadelphia chromosome positive (Ph+) relapsed or refractory B cell precursor ALL (R/R B cell ALL) should have failed treatment with at least one tyrosine kinase inhibitor (TKI).

**Dosing Information**

Inotuzumab ozogamicin should be administered in 3- to 4-week cycles. For patients proceeding to haematopoietic stem cell transplant (HSCT), the recommended duration of treatment is two cycles. A third cycle may be considered for those patients who do not achieve complete remission or complete remission with incomplete hematologic recovery (CR/CRi) and minimal residual disease negativity after two cycles. For patients not proceeding to HSCT, additional cycles of treatment, up to a maximum of six cycles, may be administered. Patients who do not achieve CR/CRi within three cycles should discontinue treatment.

For the first cycle, the recommended total dose of inotuzumab ozogamicin for all patients is 1.8mg/m² per cycle, given as three divided doses: on day 1 (0.8mg/m²), day 8 (0.5mg/m²), and day 15 (0.5mg/m²). Cycle 1 is three weeks in duration, but may be extended to four weeks if the patient achieves a CR or CRi, and/or to allow recovery from toxicity. The duration of subsequent cycles is four weeks and the recommended total dose of inotuzumab ozogamicin is 1.5mg/m² per cycle given as three divided doses: on day 1 (0.5mg/m²), day 8 (0.5mg/m²), and day 15 (0.5mg/m²) for patients who achieve a CR/CRi or 1.8mg/m² per cycle given as three divided doses on day 1 (0.8mg/m²), day 8 (0.5mg/m²), and day 15 (0.5mg/m²) for patients who do not achieve a CR/CRi.

See the summary of product characteristics (SPC) for further details concerning assessment of CD22 expression, pre-medication and administration.

Inotuzumab ozogamicin should be administered under the supervision of a physician experienced in the use of cancer therapy and in an environment where full resuscitation facilities are immediately available.

**Product availability date**

29 June 2017

Inotuzumab ozogamicin is an EMA designated orphan medicine and meets SMC ultra-orphan and end of life criteria.

**Background**

Inotuzumab ozogamicin is an antibody-drug conjugate of a recombinant humanised immunoglobulin IgG4 kappa CD22-directed monoclonal antibody covalently linked to a cytotoxic drug, N-acetyl-gamma-calicheamicin dimethylhydrazide. Its postulated novel mechanism of action is that the antibody-drug conjugate binds to and enters CD22-expressing tumour cells.
and is then cleaved by hydrolysis, releasing the cytotoxic component which induces double-stranded DNA breaks, cell cycle arrest and apoptotic cell death.\textsuperscript{2} The aim of this salvage treatment is that the patient achieves remission and is able to undergo HSCT, as this is the only potentially curative treatment option.\textsuperscript{3} The submitting company has requested that SMC considers inotuzumab ozogamicin when positioned for use in patients for whom the intent is to proceed to stem cell transplantation.

Inotuzumab ozogamicin for use in this indication has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

### Nature of condition

ALL is a malignant disease in which immature lymphoid cells undergo uncontrolled proliferation in the bone marrow, blood and other organs which causes loss of normal haematopoiesis and fatal organ failure.\textsuperscript{2} There is no definitive treatment for relapsed/refractory B cell precursor ALL and various chemotherapy salvage treatments including FLAG, FLAG plus idarubicin, high dose cytarabine, hyper CVAD (hyper-cyclophosphamide, vincristine, doxorubicin and dexamethasone) have been used. Patients with relapsed Philadelphia Chromosome positive (Ph+) ALL are offered TKIs.\textsuperscript{2,4} Blinatumomab, an antibody that causes the elimination of CD19-expressing tumour cells, has been accepted for use within NHS Scotland for the treatment of adults with Philadelphia chromosome negative (Ph-) relapsed or refractory B cell precursor ALL.\textsuperscript{5} (SMC 1145/16). The aim of salvage treatment is to induce remission, enabling allogeneic HSCT, which is the only potentially curative treatment.\textsuperscript{3} Not all patients who achieve remission will go on to receive HSCT. Some patients may decide against a transplant or not be sufficiently fit, or a donor may not be found in time. Inotuzumab ozogamicin meets SMC ultra orphan and end of life criteria.

A patient and clinician engagement (PACE) meeting was held to consider the added value of inotuzumab ozogamicin in the context of treatments currently available in NHS Scotland. At the PACE meeting, attention was drawn to the very aggressive nature of the disease and the relatively young population; median age at diagnosis is in the mid to late thirties. Median life expectancy is approximately three to six months with chemotherapy and the only possibility of long term survival is allogeneic HSCT. The high symptom burden is associated with physical difficulties (mobility, performing routine daily activities, and self-care) and there is a large negative psychological impact on patients and families. Active treatment options are limited to toxic chemotherapy which is often ineffective and blinatumomab for patients with Philadelphia chromosome negative ALL.

### Impact of new technology

#### Summary of evidence on comparative efficacy
The evidence is from a phase III open label randomised controlled study, INO-VATE 1022, that recruited adult patients with relapsed or refractory (≥5% bone marrow blasts on local morphologic analysis) CD22-positive ALL who were scheduled to receive their first or second salvage therapy.\textsuperscript{3} First salvage patients with late relapse had to be deemed poor candidates for re-induction with initial therapy. Ph+ALL patients had to have failed treatment with at least one second or third generation TKI and standard multi-agent induction chemotherapy. The proportion of patients with Ph+ disease was capped at 20% of the full study population.\textsuperscript{2,3}
Patients were randomised, stratified by duration of first remission (<12 months versus ≥12 months), phase of salvage-treatment (first versus second) and age (<55 years versus ≥55 years), in a 1:1 ratio to receive either inotuzumab ozogamicin or the investigator’s choice of one of three pre-defined regimens. Choice of standard therapy was decided after randomisation had occurred. Patients assigned to the inotuzumab ozogamicin group (n=164) received intravenous (IV) inotuzumab ozogamicin in cycle 1 at a total dose of 1.8mg/m² administered as three divided doses: 0.8mg/m² on day 1 and 0.5mg/m² on days 8 and 15. The duration of cycle 1 was 21 days. From cycle 2 onwards the cycle duration was 28 days. When a patient achieved CR/CRi the dose administered on day 1 of each subsequent cycle was reduced to 0.5mg/m² (i.e., total dose per cycle of 1.5mg/m²) for the remainder of the study. Patients were treated until disease progression or unacceptable toxicity for a maximum of six cycles. Patients who achieved complete remission could undergo stem cell transplantation at the investigator’s discretion. The most frequently used treatment in the standard therapy group was FLAG (fludarabine, cytarabine and granulocyte colony stimulating factor [G-CSF]; n=102). Patients received up to four 28-day cycles (fludarabine 30mg/m² daily on days 2 to 6; cytarabine 2g/m² daily on days 1 to 6 and G-CSF 5 micrograms/kg daily or at the standard dose of the centre). The next most common treatment was cytarabine plus mitoxantrone (n=38). Patients received up to four 15- to 20-day cycles of cytarabine 200mg/m² daily on days 1 to 7 and mitoxantrone 12mg/m² daily on days 1 to 3 (dose could be reduced to 8mg/m² due to age, co-existing conditions or previous anthracycline use). The least common standard therapy was high dose cytarabine (n=22) which was given for up to one 12-dose cycle (3g/m² every 12 hours, [1.5g/m² every 12 hours for patients ≥55 years of age]).

INO-VATE 1022 had two primary outcomes: complete remission, including complete remission with incomplete hematologic recovery (CR/CRi); and overall survival (OS). Analysis of CR/CRi was conducted in a subgroup of the intention to treat (ITT=all randomised patients) population that included the initial 218 patients (ITT218) when they had been followed for at least three months after randomisation, and it was assessed by a blinded, independent, central endpoint adjudication committee. Patients who did not achieve CR/CRi, including patients who did not receive study treatment, were considered to be non-responders. The primary analysis of OS was conducted in the ITT population (n=326) on 08 March 2016 after 252 patients had died. All patients randomised to receive inotuzumab ozogamicin received treatment, whereas 12% (19/162) of patients randomised to receive standard therapy did not receive any treatment Ten of these patients refused treatment.

The CR/CRi rate in the ITT218 population was 81% (88/109) in the inotuzumab ozogamicin group and 29% (32/109) in the standard therapy group (rate difference: 51% [97.5% confidence interval (CI): 38 to 64], Chi-square test 1-sided p-value<0.0001). The statistically significant benefit with inotuzumab ozogamicin was maintained when CR and CRi were analysed separately and also in a sensitivity analysis where the patients that withdrew prior to treatment in the chemotherapy arm were designated as responders. In a secondary analysis in the full ITT population, the CR/CRi rate was 73% (120/164) in the inotuzumab ozogamicin group and 31% (50/162) in the standard therapy group. In this analysis all patients in the inotuzumab ozogamicin group who achieved CR/CRi did so in the first three cycles; 71% in cycle 1, 26% in cycle 2 and 3.3% in cycle 3. The benefits in both CR/CRi rate and OS were independent of the pre-specified subgroups (duration of first remission [<12 months or ≥12 months], salvage treatment [first or second] or age at randomisation [<55 years or ≥55 years]).

Median OS (co-primary outcome) for inotuzumab ozogamicin compared with standard therapy was 7.7 versus 6.7 months; stratified hazard ratio (HR) 0.77 (97.5% CI: 0.58 to 1.03), p=0.020. Although this result was not statistically significant according to the pre-specified analysis, the European Medicines Agency (EMA) considered that the study approach was over conservative.
and that the result was statistically significant according to recognised statistical principles. This view is endorsed by statistical advice sought by SMC. The results in the modified ITT population (all randomised patients who started treatment, with study drug assignment designated according to initial randomisation) confirmed the statistically significant OS result when using the 1-sided p-value boundary of 0.0229 (HR 0.77 [97.5% CI: 0.57 to 1.03] and 1-sided p=0.0209. Updated OS results at the last visit of the last patient on (04 January 2017) showed a slightly greater benefit than the primary analysis: 7.7 months in the inotuzumab ozogamicin group and 6.2 months in the standard therapy group.

Secondary outcomes included progression free survival (PFS), duration of remission, lack of minimal residual disease and rate of HSCT. PFS had a non-standard definition: time from date of randomisation to earliest date of any of the following: death; progressive disease (including objective progression, relapse from CR/CRi, treatment discontinuation due to global deterioration of health status); starting new induction therapy or post-therapy HSCT without achieving CR/CRi. Median PFS, (ITT population) was significantly longer in the inotuzumab ozogamicin group, 5.0 months (95% CI: 3.7 to 5.6) than in the standard therapy group, 1.8 months (95% CI: 1.5 to 2.2); stratified HR (for disease progression, starting new induction therapy or HSCT without achieving CR/CRi or death) 0.45 (97.5% CI: 0.34 to 0.61) p<0.001. There was early separation of curves, before three months. According to the standard definition of PFS, (progressive disease or death), median PFS was 5.6 months in the inotuzumab ozogamicin group and 3.6 months in the standard therapy group. The European Public Assessment Report noted that it is possible that switch of therapy, which was more frequent in the control group, explains the longer median PFS according to the standard censoring.

Duration of remission, defined as the time from remission (investigator assessed) to progressive disease (objective progression, relapse, treatment discontinuation due to health deterioration) or death, assessed in the ITT218 population, was significantly longer in the inotuzumab ozogamicin group, median duration of remission: 4.6 months (95% CI: 3.9 to 5.4) than in the standard therapy group, 3.1 months (95% CI: 1.4 to 4.9); HR (for disease progression or death) 0.55 (95% CI: 0.31 to 0.96). An updated analysis in the ITT population where patients without remission were given a duration of zero, showed that the median duration of remission was 3.7 months (2.8 to 4.3) in the inotuzumab ozogamicin group and 0.0 months in the standard therapy group, with a stratified HR (95% CI) of 0.47 (0.36-0.60), 2-sided p<0.0001.

Of the 120 patients who had CR/CRi from the ITT218 population, a significantly higher proportion in the inotuzumab ozogamicin group 78% (69/88) than in the standard therapy group 28% (9/32) had results below the threshold for minimal residual disease (0.01% marrow blasts); difference between treatment groups was 50.3% (97.5% CI: 29.9 to 70.6) p<0.001.

The proportion of patients from the ITT218 population who underwent HSCT directly after study treatment was significantly higher in the inotuzumab ozogamicin group than in the standard therapy group: 41% (45/109) versus 11% (12/109), p<0.001. The proportion of patients from the ITT population who underwent HSCT was 47% (77/164; [71 patients directly after study treatment; six patients required further salvage treatment]) in the inotuzumab ozogamicin group) and 20% (33/162; 18 patients directly after study treatment; 15 patients required further salvage treatment ) in the standard therapy group.

Health related quality of life was assessed using the European Organisation for Research and treatment of Cancer Quality of Life core questionnaire EORTC QLQ-C30, the EuroQol 5 dimension (EQ-5D) Index, and the EuroQol visual analogue scale (EQ-VAS). There were substantially more missing data in the standard therapy group (35%) than the inotuzumab ozogamicin group (15%). There were no significant differences between the treatment groups.
for the EQ-5D or EQ-VAS. There was a statistically significant improvement in four components of the EORTC QLQ-C30: physical functioning, role functioning, social functioning and appetite loss. It is not clear if any of these improvements were also clinically significant.

Summary of evidence on comparative safety
In the INO-VATE 1022 study, at the 8 March 2016 cut off, median treatment duration was longer in the inotuzumab ozogamicin group than in the standard therapy group (8.9 weeks, corresponding to three cycles versus 0.9 weeks, corresponding to one cycle). Adverse events were reported in 99% (163/164) of patients in the inotuzumab ozogamicin group and in 100% (143/143) in the standard therapy group; and these were considered to be treatment related in 88% and 91% of patients, respectively. Serious adverse events were reported in 51% of patients in the inotuzumab ozogamicin group and in 50% in the standard therapy group; and these were considered to be treatment related in 31% and 29% of patients, respectively. Higher proportions of patients in the inotuzumab ozogamicin than the standard therapy group: discontinued treatment due to treatment related adverse events (9.1% versus 4.9%); delayed treatment due to treatment related adverse events (31% versus 8.4%) and had dose reductions due to treatment related adverse events (2.4% versus 0.7%).

Serious (including life-threatening or fatal) infections were reported in 48% (79/164) of inotuzumab ozogamicin-treated patients; sepsis and bacteraemia (16%), lower respiratory tract infection (12%), upper respiratory tract infection (12%), fungal infection (9%), viral infection (8%), gastrointestinal infection (4%), skin infection (4%), and bacterial infection (1%).

Veno-occlusive liver disease/sinusoidal obstruction syndrome (VOD/SOS) occurred in 13% (22/164) of patients receiving inotuzumab ozogamicin and five of these patients had not undergone HSCT after study treatment (two out of the five patients had undergone HSCT prior to study entry). At the 8 March 2016 cut off, 77 patients in the inotuzumab ozogamicin group had undergone HSCT after study treatment, and six of these patients had received additional salvage therapy after inotuzumab ozogamicin and before HSCT. VOD/SOS was reported in 22% (17/77) of these patients and was fatal in five patients. Risk factors include subsequent HSCT (especially if the conditioning regimen includes two alkylating drugs), older age and raised serum bilirubin before HSCT. Other factors that seem to be associated with an increased risk of VOD/SOS after HSCT include a prior HSCT, a history of liver disease/hepatitis before treatment, later salvage lines, and a higher number of treatment cycles.

Treatment related deaths occurred in 5.5% (9/164) of patients in the inotuzumab ozogamicin group: VOD/SOS after follow-up HSCT (n=5 as noted above); intestinal ischaemia/septic shock, after cycle 5 (n=1); acute respiratory distress, after cycle 3 (n=1), pneumonia, after cycle 5 (n=1) and multi-organ failure, after cycle 5 and HSCT, with ongoing SOS (n=1). Treatment related deaths occurred in 2.1% (3/143) of patients in the standard therapy group: intracranial haemorrhage (n=1); multi-organ failure (n=1) and lung infection/ respiratory failure (n=1).

The SPC notes the need for appropriate precautions and close monitoring for the following adverse events: hepatotoxicity, including potentially fatal VOD/SOS, myelosuppression, infusion related reactions, potentially fatal tumour lysis syndrome, QT interval prolongation.
Summary of clinical effectiveness issues
The submitting company has requested that SMC considers inotuzumab ozogamicin when positioned for use in patients intended to receive subsequent HSCT.

The INO-VATE 1022 study (ITT analyses) demonstrated that patients who received inotuzumab ozogamicin compared with standard therapy achieved a statistically and clinically significantly higher rate of CR/CRi (73% versus 31%), improved median OS and higher rates of directly proceeding to HSCT without further salvage treatment (43% versus 11%), respectively.\(^2\) OS is the most relevant outcome but is confounded by other factors including subsequent anti-cancer treatments, availability of a suitable HSCT donor and complications of HSCT.\(^3\) In the pivotal study, at the 8\(^{th}\) March 2016 data cut-off, although 120 patients in the inotuzumab ozogamicin group had achieved CR/CRi, only 71 patients in this treatment group underwent transplant directly after study treatment.\(^2\)

The proposed positioning is for patients intended for HSCT, which requires a maximum of three treatment cycles. The proportion of patients in the pivotal study that represents the proposed positioning is unclear, however all patients in the ITT population who achieved CR/CRi did so within the first three cycles, and the vast majority achieved this in the first (71%) or second (26%) cycle.\(^2\)

There was no evidence comparing inotuzumab ozogamicin with FLAG+idarubicin which clinical experts consulted by SMC have advised has been used in this patient population in Scotland. The evidence versus blinatumomab in Ph- patients is indirect.

The open label design of the study was unavoidable but may have introduced bias as there was a higher proportion of patients in the standard chemotherapy group who did not receive any study treatment. The standard therapy group included three treatments and the choice was at the discretion of the investigator. There was no subgroup analysis according to choice of treatment and the relative efficacy of each treatment regimen is not known.

The European Society for Medical Oncology (ESMO) guidelines recommend that Ph+ALL patients with persistent minimal residual disease or progressive disease switch to another TKI while screening for TKI resistance mutations and adapt the TKI choice according to the resistance profile. A total of 57\% (28/49) of the patients in the study with Ph+ALL had received only one prior TKI and four had not received any.\(^2\)

The submitting company noted that, in practice, there may be slightly higher rates of patients with prior HSCT (due to a second HSCT being funded in Scotland) and slightly higher rates of Ph+ patients than observed in the study.

There is no direct comparative evidence versus blinatumomab which is now available in Scotland for Ph- patients. The submitting company presented a matching adjusted indirect comparison (MAIC) as the main indirect comparison. An anchored simulated treatment comparison and a Bucher comparison were also presented. All three indirect comparisons included one study comparing inotuzumab ozogamicin with chemotherapy (INO-VATE 1022) and one study comparing blinatumomab with chemotherapy (TOWER).\(^3,\)\(^6\) The population was adult patients with Ph- B cell precursor ALL. The comparator arms in both studies was investigator’s choice from a variety of chemotherapy regimens. The outcome measures reported for the MAIC were CR/CRi rate, HSCT rate, event-free survival, OS and adverse events.
The key weaknesses of this indirect comparison include the small number of patients analysed; differences in the common comparator arm; difference in the median duration of OS in the control arm of INO-VATE 1022 compared with TOWER (TOWER was stopped prematurely and therefore the follow up time was very short); some treatment-effect modifiers were not adjusted for the analyses and not all patient baseline characteristics could be accurately matched. Also, MAIC analyses in general have known limitations including confounding by unobserved differences between studies.

Clinical experts consulted by SMC considered that inotuzumab ozogamicin is a therapeutic advancement due to the lack of effective treatments for this condition. Inotuzumab ozogamicin would provide an advantage over current chemotherapy regimens or blinatumomab which require hospitalisation as it can be administered in the outpatient setting with the patient treated as a day case. This would be beneficial to the patient and family in terms of convenience and quality of life as well as to the service.

Some patients may be initially intended for HSCT and, after three treatment cycles, do not have a suitable donor or are no longer sufficiently fit for transplant or who decide against it.

At the PACE meeting, it was noted that inotuzumab ozogamicin is a novel treatment that acts as a bridge to potentially curative HSCT through significantly higher remission rates than chemotherapy and consequent increased likelihood of a transplant. Improved PFS and OS compared with chemotherapy, provides additional quality time for patients and families which is viewed as extremely beneficial. PACE participants highlighted potential benefits over both chemotherapy and blinatumomab in terms of safety and reduced hospitalisation. Inotuzumab ozogamicin may also provide an active treatment option for older patients who are not sufficiently fit to tolerate chemotherapy.

Other data were also assessed but remain commercially confidential.*

Patient and clinician engagement

A PACE meeting with patient group representatives and clinical specialists was held to consider the added value of inotuzumab ozogamicin as an ultra-orphan and end of life medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Relapsed or refractory ALL is a rare, very aggressive disease affecting a relatively young population. Median life expectancy is less than six months with standard care. The symptom burden is high and can result in difficulties in mobility, performing routine daily activities, and self-care, in addition to a large negative psychological impact on patients and their families.

- Active treatment options are limited to toxic chemotherapy and, for Philadelphia chromosome negative patients, blinatumomab. Chemotherapy is often ineffective and most patients are unable to go on to receive a transplant, despite experiencing severe adverse effects and often spending around half of their limited remaining time in hospital. PACE participants noted that blinatumomab has a complex administration schedule and requires some periods of hospitalisation.
• Inotuzumab ozogamicin has been shown to be an effective salvage treatment for relapsed/refractory ALL as it significantly improves remission rates compared with standard care. It acts as a bridge to the only potential cure, HSCT. It may also provide an active treatment option for older patients who are not sufficiently fit to tolerate chemotherapy. The benefit in PFS and OS over chemotherapy provides a high relative gain in the context of limited remaining months. Use of inotuzumab ozogamicin would avoid many of the adverse effects caused by chemotherapy. As it can be delivered in an outpatient setting, patients are less likely to require hospitalisation than those receiving chemotherapy or blinatumomab. This highly valued additional time can therefore be spent at home.

• As inotuzumab ozogamicin has the potential to increase the risk of veno-occlusive disease, risk factors have to be considered by clinicians before treatment initiation and liver function needs to be closely monitored.

• The place of inotuzumab ozogamicin in therapy is in patients for whom the intent is to proceed to stem cell transplantation as this provides the only possibility of long term survival.

Additional Patient and Carer Involvement
We received a patient group submission from Leukaemia CARE. Leukaemia CARE is a registered charity. Leukaemia CARE has received 11.6% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Leukaemia CARE participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Value for money

The company submitted a cost-utility analysis which compared inotuzumab ozogamicin against chemotherapy standard of care (SoC) in adult patients with R/R B-cell ALL in whom the intent is to proceed to stem cell transplantation. SoC consisted of FLAG, cytarabine plus mitoxantrone, high-dose cytarabine and an additional cost attributed to dasatinib for Ph+ patients. A sensitivity analysis versus blinatumomab was also provided by the company for patients who were Ph-.

A Markov model was used to evaluate the cost-effectiveness of inotuzumab ozogamicin versus the comparators. In terms of model structure patients entered the model at baseline and could move to the following health states: no CR/CRi and no HST, CR/CRi and no HSCT, and HSCT and post HSCT, depending on response to treatment. Within each of these health states PFS and OS were modelled in order to capture survival outcomes associated with that particular health state. The time horizon for the analysis was 60 years, and the model used a maximum treatment duration of three cycles of inotuzumab ozogamicin.

Clinical data were taken from the INO-VATE 1022 study and a MAIC. The INO-VATE 1022 study was used to provide data for inotuzumab ozogamicin in the base case analysis with data for SoC being taken from the investigator’s choice arm of the same study. For the comparison versus blinatumomab, data for inotuzumab ozogamicin were taken from the Ph- subgroup of INO-VATE 1022 while the relative efficacy of blinatumomab was informed by the MAIC. The economic model included a number of clinical variables such as response rates (which informed the health state patients would transition in to), and PFS and OS estimates for each health state which included extrapolation of trial data over the period of the time horizon using parametric functions. The HSCT rates used in the economic evaluation reflected rates which included the...
impact of subsequent therapies, as opposed to transplant rates from directly after discontinuing inotuzumab ozogamicin or SoC. For patients who entered the HSCT and post HSCT health state (i.e. went on to receive a transplant) a cure assumption was included in the economic model. Specifically the cure assumption was applied to patients who were alive and progression-free three years after transplant, and assumed the risk of death switches to 3.5 times that of the general population at this point.

Utility values were derived from EQ-5D data collected within the INO-VATE 1022 study and supplemented with utility estimates from published sources. The utility values were as follows: baseline 0.69, no CR/CRi and no HST 0.53, CR/CRi and no HST 0.76, post HSCT <1 year 0.59, post HSCT 1-2 years 0.75, post cure 0.87 (reflective of general population utility + age adjustments), progression (for all progressed disease states in model) 0.30. Disutilities due to adverse events were not included in the analysis apart from the occurrence of VOD for patients who underwent a HSCT. The disutility of graft versus host disease (GvHD) was assumed to be captured in the post HSCT utilities referenced above which were taken from a published study.

Medicine costs were included in the analysis as well as the cost of administration, transplant, adverse events, subsequent treatment, and end of life.

A Patient Access Scheme (PAS) was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. A PAS is in place for blinatumomab and this was included in the results used for decision-making by the SMC by using an estimate of the PAS price of blinatumomab.

The base case results and selected sensitivity analyses with the PAS for inotuzumab ozogamicin are presented in Table 1 below. However please note that the results presented do not take account of the PAS for blinatumomab, but this was considered in the results used for decision-making at SMC. SMC is unable to present the results provided by the company which used an estimate of the PAS price for blinatumomab due to commercial confidentiality and competition law issues and hence the results are presented for this comparison using the list price of both inotuzumab ozogamicin and blinatumomab.

Table 1: Base case results and selected sensitivity analysis (with PAS for inotuzumab ozogamicin unless stated)

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The main weaknesses were

- An important component of the economic model related to capturing the proportion of patients who moved on to HSCT as well as the proportion of patients who achieved CR/CRi but no HSCT, and those who did not achieve a CR/CRi and did not proceed to HSCT. However the proportion of patients who achieved a HSCT was not the primary endpoint of the pivotal study and it may not be possible to conclude that the difference in HSCT rates between inotuzumab ozogamicin and the comparator is solely down to treatment. This is because other factors may influence the results such as patient preference, donor availability, fitness, and potentially other unknown factors.

- A similar weakness as above can also be extended to the modelling of OS, and PFS for each treatment in each health state. At this point in the model randomization has been lost and it is difficult to determine whether the patients in each health state were sufficiently similar to determine whether, for example, OS would be improved for patients who underwent a HSCT having previously been treated with inotuzumab ozogamicin versus SoC. The company has provided a sensitivity analysis which modelled no difference in PFS and OS between treatment arms post-HSCT, combined with using HSCT rates from immediately after the stopping study therapy, and removed the cost of subsequent therapies which enabled patients to transition to transplant after stopping initial therapy. The results are available in Table 1 above.

- The model used the Gompertz function to extrapolate PFS and OS over the longer term for HSCT and the Gompertz curve for both variables flattens at around 2 years. The company commented that the Gompertz function captured an expected plateau in the survival estimates, however it is uncertain whether the survival estimates are overly optimistic. The company has provided a sensitivity analysis which uses the generalised gamma function for both PFS and OS and the results are available in Table 1 above.

- In terms of the costs used in the analysis, the model included patients who achieved a CR/CRi but did not proceed to transplant, therefore the analysis imposed a maximum treatment duration of 3 cycles on these patients although they may receive up to 6 cycles in clinical practice.

Other data were also assessed but remain commercially confidential.*

Impact beyond direct health benefits and on specialist services

Improvements in disease control and a reduction in the time spent in hospital are likely to reduce the emotional burden on their family and friends. Treatment with inotuzumab ozogamicin, compared with chemotherapy, is expected to have less impact on a carer’s ability to work as, apart from regular outpatient clinic visits, patients are likely to be self-caring at home.
Small patient numbers are anticipated; approximately five to ten patients per year and most patients are expected to receive two or three cycles of treatment. Compared with chemotherapy or blinatumomab, treatment with inotuzumab ozogamicin is expected to benefit the service by a reduction in the need for in-patient beds.

### Costs to NHS and Personal Social Services

The submitting company estimated there would be nine patients eligible for treatment with inotuzumab ozogamicin in all years to which confidential uptake rates were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain commercially confidential.*

### Conclusion

The Committee also considered the benefits of inotuzumab ozogamicin in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that a number of the criteria were satisfied: a substantial improvement in quality of life and the potential to bridge to a definitive therapy. In addition, as inotuzumab ozogamicin is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted inotuzumab ozogamicin for restricted use in NHS Scotland.

### Additional information: guidelines and protocols

Guidance was published in 2016 on behalf of the European Society for Medical Oncology: Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. It notes that there is no universally accepted treatment protocol for relapsed/refractory ALL but that treatment with a curative aim involves achievement of CR followed by allogeneic stem cell transplant. The guideline notes that the most commonly used chemotherapy regimens in Europe are fludarabine- and anthracycline-containing regimens, for example, FLAG-Ida (fludarabine, high-dose cytarabine, granulocyte colony-stimulating factor and idarubicin).4

The guideline was written before the availability of inotuzumab ozogamicin or blinatumomab.

### Additional information: comparators

Chemotherapy regimens including FLAG and FLAG-IDA); blinatumomab in Ph-ALL patients.
## Cost of relevant comparators

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dose Regimen</th>
<th>Cost per cycle (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Inotuzumab ozogamicin</em></td>
<td>IV infusion&lt;br&gt;Cycle 1 (3-week cycle): day 1 (0.8mg/m²), day 8 (0.5mg/m²), day 15 (0.5mg/m²)&lt;br&gt;Cycle 2: (4-week cycle) day 1 (0.5mg/m² if CR/CRi already achieved; 0.8mg/m² if CR/CRi not already achieved), day 8 (0.5mg/m²), day 15 (0.5mg/m²)&lt;br&gt;Cycle 3 (if required): (4-week cycle) day 1 (0.8mg/m²), day 8 (0.5mg/m²), day 15 (0.5mg/m²)</td>
<td>Cycle 1: 32,192&lt;br&gt;Cycle 2: 24,144 or 32,192&lt;br&gt;Cycle 3: (if required) 32,192</td>
</tr>
<tr>
<td><em>Blinatumomab</em>*</td>
<td>IV infusion&lt;br&gt;Cycle 1&lt;br&gt;Days 1 to 7: 9 micrograms/day&lt;br&gt;Days 8 to 28: 28 micrograms/day&lt;br&gt;14 day treatment free period&lt;br&gt;Subsequent cycles (Day 1 to 28)&lt;br&gt;28 micrograms/day</td>
<td>Cycle 1: 48,408&lt;br&gt;Subsequent cycles: 56,476</td>
</tr>
<tr>
<td><strong>FLAG</strong>*</td>
<td>Fludarabine 30mg/m² IV daily on days 2 to 6&lt;br&gt;Cytarabine 2000mg/m² IV infusion daily on days 1 to 6&lt;br&gt;Filgrastim (G-CSF) 5 micrograms/kg subcutaneously daily (for up to 14 days)</td>
<td>Up to 3,540</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online (except for granulocyte colony stimulating factor from eVADIS) on 05.02.18. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration. Doses based on body surface area of 1.8m² and body weight of 70kg.

*IV=intravenous<br>*Doses and costs are for proposed positioning (maximum of three treatment cycles).<br>**Philadelphia chromosome negative ALL only, recommended dose for patients at least 45kg in weight<br>***FLAG=fludarabine, cytarabine and granulocyte colony stimulating factor (G-CSF). Dose regimen from INO-VATE 1022 study.³<br>FLAG-IDA: Adding idarubicin to the FLAG regimen, at a dose of 8mg/m² (intravenous bolus) for three days, gives a total cost for the regimen of up to £4,326 per cycle; (dose of idarubicin from SMC 1145/16 advice).
References


This assessment is based on data submitted by the applicant company up to and including 16 March 2018.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:
http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the
considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.