SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
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NHS SCOTLAND
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gemtuzumab ozogamicin 5mg powder for concentrate for solution for infusion (Mylotarg®) SMC No2089

Pfizer Ltd

7 September 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 end of life and orphan medicine process

gemtuzumab ozogamicin (Mylotarg®) is accepted for restricted use within NHSScotland.

Indication under review: For combination therapy with daunorubicin and cytarabine for the treatment of patients age 15 years and above with previously untreated, de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia (APL).

SMC restriction: use in patients with a favourable, intermediate or unknown cytogenetic profile.

In an open-label, phase III study of adults with AML, the addition of gemtuzumab ozogamicin to standard intensive chemotherapy was associated with significant improvement in event-free survival compared with standard intensive chemotherapy alone. Events included failure to achieve remission with induction therapy, relapse of disease, or death.

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

Chairman,
Scottish Medicines Consortium

Indication

For combination therapy with daunorubicin and cytarabine for the treatment of patients age 15 years and above with previously untreated, de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia (APL).[1]

Dosing Information

Gemtuzumab ozogamicin should be administered under the supervision of a physician experienced in the use of anticancer medicinal products and in an environment where full resuscitation facilities are immediately available.

Gemtuzumab ozogamicin should be used only in patients eligible to receive intensive induction chemotherapy.

Premedication with a corticosteroid, antihistamine, and acetaminophen (or paracetamol) is recommended 1 hour prior to dosing to help ameliorate infusion-related symptoms.

In patients with previously untreated AML, the dose of gemtuzumab ozogamicin is as follows:

Phase of treatment	Dosage schedule		
	gemtuzumab ozogamicin	daunorubicin	cytarabine
Induction	3mg/m^2 per day (maximum of one 5mg vial) days 1, 4 and 7.≠	60mg/m^2 per day days 1 to 3	200mg/m^2 per day days 1 to 7
Consolidation± (up to two courses)	3mg/m^2 per day (maximum of one 5mg vial) day 1	60mg/m^2 per day day 1 (course 1) days 1 and 2 (course 2)	1g/m^2 every 12 hours days 1 to 4

≠gemtuzumab ozogamicin should not be administered during a second course of induction.
±consolidation treatment for patients experiencing complete remission following induction therapy.

Please refer to the summary of product characteristics for advice on dose and schedule adjustment for hyperleukocytosis, adverse reactions, and in special populations.[1]

Product availability date

25 April 2018.

Gemtuzumab ozogamicin meets SMC orphan and end of life criteria for this indication.

Summary of evidence on comparative efficacy

Gemtuzumab ozogamicin is an antibody-drug conjugate (ADC) combining a humanised anti-CD33 antibody with the cytotoxic small molecule N-acetyl gamma calicheamicin. The ADC binds to CD33-expressing tumour cells. Following internalisation of the ADC-CD33 complex, there is intracellular release of N-acetyl gamma calicheamicin. N-acetyl gamma calicheamicin induces double-stranded DNA damage which leads to apoptosis and cell death.[1]

The submitting company has requested that SMC considers gemtuzumab ozogamicin when positioned for use in patients with a favourable, intermediate or unknown cytogenetic profile.

The key evidence is the phase III, multi-centre, randomised, open-label, Acute Leukaemia French Association study, ALFA-0701.[2, 3] The study recruited 280 adults (aged 50 to 70 years of age) with a confirmed diagnosis of acute myeloid leukaemia (AML) that was not previously treated. Patients were eligible for inclusion if they had an Eastern Co-operative Oncology Group (ECOG) performance status of 0 to 3, normal cardiac function as assessed by use of radionucleotide scintigraphy or echography, and blood and bone marrow specimens taken for molecular assessment.

Patients were stratified by study centre and randomised in a 1:1 ratio to standard intensive chemotherapy with or without gemtuzumab ozogamicin (Table 1). Premedication with antihistamine and methylprednisolone was given prior to gemtuzumab ozogamicin administration.

Treatment comprised two phases,induction and consolidation. Patients advanced from the induction to the consolidation phase following achievement of complete remission (CR) or CR with residual thrombocytopenia (CRp). CR was defined as absence of leukaemic blast cells in blood and disappearance of all tumours, <5% blasts in the bone marrow, haemoglobin >90g/L, absolute neutrophil count >1.0x10^9/L, and platelet count >100x10^9/L and transfusion independence; CRp was CR with incomplete recovery of the platelet count. A second induction course was indicated for patients with bone marrow blasts >10% (or >5% following protocol amendment) on day 15.

Patients who did not achieve CR after the first course of induction could receive salvage therapy at the investigator's discretion, provided the patient had a creatinine clearance >30mL/min and ECOG performance status <3. Salvage comprised idarubicin 12mg/m^2 (days 1 and 2), cytarabine 1g/m^2 every 12 hours (days 1 to 4), and granulocyte-colony stimulating factor (starting on day six). Patients who failed to achieve CR or CRp after the second induction or after salvage therapy, had treatment discontinued.

Table 1: Treatment regimen for ALFA-0701[3]

Phase of treatment	Standard chemotherapy	Randomised treatment
Induction course 1	daunorubicin 60mg/m^2 IV (days 1 to 3) cytarabine 200mg/m^2 IV (days 1 to 7)	gemtuzumab ozogamicin 3mg/m^2 IV (days 1, 4 and 7) or nothing
Induction course 2	daunorubicin 35mg/m^2 IV (days 1 and 2) cytarabine 1g/m^2 IV every 12 hours (days 1 to 3)	nil
Consolidation course 1	daunorubicin 60mg/m^2 IV (day 1) cytarabine 1g/m^2 IV every 12 hours (days 1 to 4)	gemtuzumab ozogamicin 3mg/m^2 IV (day 1) or nothing
Consolidation course 2	daunorubicin 60mg/m^2 IV (days 1 and 2) cytarabine 1g/m^2 IV every 12 hours (days 1 to 4)	gemtuzumab ozogamicin 3mg/m^2 IV (day 1) or nothing

The treatment schedule was adjusted in cases of hyperleukocytosis; hydroxycarbamide was used for cytoreduction, tumour lysis syndrome prophylaxis was mandated, and cytarabine was commenced two days earlier than daunorubicin and gemtuzumab ozogamicin.

Use of stem-cell transplantation could be considered for patients who experienced CR and who were categorised with intermediate II or unfavourable cytogenetic and molecular risk categories. Pre-transplant conditioning was not specified and was at the discretion of the transplant centre; an interval of two months between transplant and last dose of gemtuzumab ozogamicin was recommended.[2, 3]

The primary outcome was event-free survival (EFS), defined as the time from randomisation to the date of induction failure, relapse, or death. Date of induction failure was defined as date of marrow evaluation after the last course of induction if CR or CRp had not been achieved. Events were assessed by local investigators and disease progression was classified in accordance with International Working Group criteria.[2, 3]

The key publication presents results for the intention-to-treat (ITT) population (all randomised patients, n=278) at a data cut-off in August 2011.[2] However, the regulatory assessment was based on analysis in the modified intention to treat (mITT) population which comprised all ITT patients except nine patients who had missing informed consent documents (n=271). Retrospective analyses were also performed by a blinded independent review committee (BIRC).[3]

At the data cut-off for the primary analysis (August 2011), gemtuzumab ozogamicin was associated with a significant improvement in EFS in the mITT population (Table 2). In an updated, retrospective analysis of the mITT populations, based on BIRC assessment at a data cut-off in April 2013, the hazard ratio (HR) for EFS was 0.71 (95% confidence interval [CI]: 0.54 to 0.93), p=0.012.[3]

Secondary outcomes included overall survival, response rates (proportion achieving either CR or CRp), and relapse-free survival (time from achievement of remission, either CR or CRp, to the first of relapse or death form any cause). Results are reported for the mITT population (n=271) and for the subgroup of patients with favourable or intermediate Medical Research Council (MRC) cytogenetic risk profiles (n=189) in Table 2.

Table 2: Primary and secondary outcomes of ALFA-0701 (investigator-assessment) for the mITT population, and subgroup relevant to indication under review.[1, 3]

Outcome		mITT		Favourable or intermediate cytogenetic risk	
		gemtuzumab ozogamicin group (n=135)	control group (n=136)	gemtuzumab ozogamicin group (n=94)	control group (n=95)
Event Free Survival	Event rate	54%	75%	47%	72%
	Median EFS	17.3 months	9.5 months	22.5 months	11.6 months
	HR (95% CI)	0.56 (0.42 to 0.76), p=0.0002		0.46 (0.31 to 0.68), p<0.0001	
Overall survival	Event rate	59%	65%	54%	60%
	Median OS	27.5 months	21.8 months	38.6 months	26.0 months
	HR (95% CI)	0.81 (0.60 to 1.09), p=0.16		0.75 (0.51 to 1.09), p=0.13	
Response rate	Proportion achieving remission (CR or CRp)	81% (110/135)	74% (100/136)	NR	NR
	Odds ratio (95% CI)	1.58 (0.86 to 2.96), p=0.15		NR	
Relapse-free survival	Event rate	45% (49/110)	66% (66/100)	NR	NR
	Median RFS	28.0 months	11.4 months	NR	NR
	HR (95% CI)	0.53 (0.36 to 0.76), p=0.0006		NR	

Data cut-off for all outcomes was August 2011, except overall survival (April 2013). EFS = event-free survival, OS= overall survival, RFS = relapse free survival, HR = hazard ratio, CI = confidence interval, CR = complete remission, CRp = complete remission with incomplete recovery of platelet count, NR = not reported.

The company's economic case was based on the retrospective BIRC review of the subgroup of patients with favourable or intermediate cytogenetic risk at a data cut-off in April 2013.

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

Summary of evidence on comparative safety

In the as-treated population of the ALFA-0701 study (n=268), the majority of patients experienced a treatment-related adverse event (AE): 98% (129/131) of patients in the gemtuzumab ozogamicin group, and 92% (126/137) of patients in the control group. Treatment-related AEs that were grade 3 or 4 or severe infections, were reported in 87% and 76% of patients, respectively. The proportions of patients who discontinued study treatment due to a treatment-related AE were 29% and 2.9%, respectively.[3]

The most common all-causality, grade 3 or 4, AEs were: infections and infestations (78% of gemtuzumab ozogamicin-treated patients and 77% of control-treated patients), haemorrhage (21% and 8.8% respectively), nausea or vomiting or diarrhoea (17% and 10%), mucosal toxicity (16% and 6.6%), pain (15% and 3.6%), pulmonary toxicity (13% and 14%), and skin toxicity (11% and 17%).[3]

Grade 3 or 4 veno-occlusive disease occurred in three gemtuzumab ozogamicin-treated patients and in two control-treated patients.[3]

Fatal treatment-related AEs occurred in 5.3% (7/131) of gemtuzumab ozogamicin-treated patients and 3.6% (5/137) of control-treated patients. The mechanism of deaths in the gemtuzumab ozogamicin group were reported as haemorrhage (n=4), liver toxicity (n=2), infection (n=1), septic shock (n=1), disease progression or relapse (n=1) or other (n=3).[3]

Safety data in the subpopulation of patients with favourable / intermediate cytogenetics profile were consistent with the overall as-treated population.

Summary of clinical effectiveness issues

AML is a heterogeneous group of haematopoietic stem cell disorders characterised by incomplete maturation of blood cells and decreased production of normal haematopoietic elements.

Symptoms commonly experienced by patients, resulting from the associated pancytopenia, include fatigue, dyspnoea, infection and bleeding.[5] Prognosis at the point of diagnosis is affected by patient and AML-related factors. With respect to patient factors, increasing age, poorer performance status, and poor general health adversely affect prognosis. Hyperleukocytosis at presentation, and cytogenetic abnormalities such as FLT3-mutation are associated with poorer prognosis.[6, 7] Long-term survival is around 5 to 15% in those over 60 years of age, and 35 to 40% in younger patients.[3] Median OS in control group of ALFA-0701 was 26 months for patients with a favourable or intermediate cytogenetic risk profile.

The majority of patients are offered participation in clinical trials such as the collaborative AML studies (eg AML 18, and 19). Choice of treatment is determined by the fitness of the patient to receive intensive induction chemotherapy; this includes a risk assessment of treatment-associated mortality, particularly in older patients, those with poorer performance status, or complicating co-morbidities. Patients with adverse cytogenetics or molecular genetics may not be considered good candidates for intensive treatment on the balance that the benefits

may be reduced to the extent that they do not outweigh the associated risks of treatment. Intensive treatment is given with curative intent. Patients considered not suitable for intensive induction therapy are managed with palliative systemic treatment such as low-dose cytarabine, or entry into clinical trials, or with best supportive care (which may include hydroxycarbamide to manage leukocytosis). For those considered eligible, intensive induction regimen comprising three days of an anthracycline (eg daunorubicin) and seven days of cytarabine in a 21-day cycle, commonly referred to as a '3+7' regimen are recommended in European AML guidelines. Consolidation therapy is indicated upon clinical and haematological remission and may include stem-cell transplant. [6, 7]

Gemtuzumab ozogamicin meets SMC orphan and end-of-life criteria for this indication.

The submitting company has requested that SMC considers gemtuzumab ozogamicin when positioned for use in in patients with a favourable, intermediate, or unknown cytogenetic profile.

The ALFA-0701 study found that addition of gemtuzumab ozogamicin to standard induction chemotherapy (daunorubicin plus cytarabine) was associated with significant clinical benefit in terms of EFS. EFS is a composite measure of effectiveness; events captured include failure to achieve remission (ie failure to achieve either CR or CRp), disease relapse for those who achieve a response and death from any cause. The secondary outcomes pointed to delayed disease relapse as the main driver for the benefit of improved EFS. There was no difference in response rates and no significant difference in overall survival between treatment groups. However, a published meta-analysis that pools evidence from multiple trials has shown significant OS gains.[10] Subgroup analyses of EFS suggest there is no benefit of adding gemtuzumab ozogamicin to standard chemotherapy, in patients with unfavourable cytogenetic profile (HR 1.11, investigator-assessment, August 2011);[1, 3] whereas there was a significant benefit in the subgroup with favourable or intermediate cytogenetic risk (HR 0.46, table 2).

No patient-reported outcomes were measured during the study.

The European Medicines Agency (EMA) noted that there was a high rate of protocol deviations reported in approximately 50% (n=139) of patients. The majority of deviations were study treatment dosing errors (30 patients with a gemtuzumab ozogamicin error, and 68 patients with an error of chemotherapy dosing). In addition 22 patients had eligibility criteria deviations. The EMA was concerned about the robustness of the study documentation and therefore of the primary data. It was reassured, given the range of sensitivity analyses used to analyse the results.[3] An independent review committee provided a blinded assessment of outcomes, mitigating the open-label design of the study, and potential bias from un-blinded local investigators, although it should be noted that this was retrospective.

The most recent data cut-off was from 2013; it is unclear if contemporary, and more mature data are available.

The dosing schedule of standard chemotherapy (daunorubicin plus cytarabine) was "3+7" in the ALFA-0701 study. In NHSScotland, daunorubicin plus cytarabine is offered to patients who are not recruited into clinical studies (eg AML18 and AML19), the regimen used tends to be a "3+10, 3+8" schedule. British guidelines have noted that there is no evidence that cytarabine given for 10 days is superior to a 7-day course.[8]

ALFA-0701 recruited patients aged 50 to 70 years of age, however the full licensed population includes patients from age 15 years. In NHSScotland, the majority of patients diagnosed with AML

are over 50 years of age; in 2016, the interquartile range for age at diagnosis was 55 to 84 years.[9] The EMA extrapolated the findings of the ALFA-0701 study to cover the full licensed population, reasoning that there was disease similarity across the patient groups, evidence from other studies showed that there were no outcome differences between teenagers and young adults and adult patients, pharmacokinetic data support similar exposure between adults and adolescents and evidence to support the impression that teenagers and young adults tend to tolerate intensive chemotherapy better than older patients.[3]

The company's subgroup analysis did not include patients with unknown cytogenetic risk who would also be eligible for gemtuzumab ozogamicin within the proposed positioning. Patients with unknown cytogenetic risk comprised 9.2% (25/271) of the mITT population of the study. Expert opinion suggests that cytogenetic results are often not known at the time first dosing is required.

Clinical experts consulted by SMC considered that the addition of gemtuzumab ozogamicin to remission induction treatment would offer a therapeutic advancement due to improved response and durability of treatment. Patients undergoing intensive chemotherapy tend to be managed as inpatients, addition of gemtuzumab ozogamicin is unlikely to alter this practice.. The service has experience of using gemtuzumab ozogamicin within the context of the collaborative AML studies. The dosing regimen for induction and consolidation recommended in the marketing authorisation for gemtuzumab ozogamicin is different and would require careful introduction of this new dosing regimen to avoid medication errors. The majority of patients diagnosed with AML are recruited to clinical studies; the impact of "off-trial" gemtuzumab ozogamicin availability, is unclear.

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

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of gemtuzumab ozogamicin, as an orphan / end-of-life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- AML is a devastating disease with a particularly poor prognosis, and significant symptom burden. In addition there are important emotional and financial stresses that have considerable impact on patients, their families and carers, including the fear of disease relapse in those who achieve remission.

- Standard intensive chemotherapy regimens are associated with significant toxicities and can be debilitating for patients. For those who achieve remission, there is a high risk of relapse.

- Gemtuzumab ozogamicin is considered to be an important therapeutic advancement for a disease which has had limited improvements in treatment over the last 20 to 30 years.

- Gemtuzumab ozogamicin is expected to prolong time in remission and relapse-free survival with a relatively small increase in toxicity, and therefore offers patients an extended period of time before quality of life is reduced by disease symptoms or side-effects associated with chemotherapy. The improvement in patient quality of life is expected to translate to a wider positive impact on the lives of family and friends.

- PACE participants felt that gemtuzumab ozogamicin was appropriately positioned for use in patients with favourable, intermediate, or unknown cytogenetic risk. It was noted that due to clinical urgency patients often require to commence treatment before the level of cytogenetic risk is known; clinicians indicated that treatment started in such patients would be reviewed and modified if necessary.

Additional Patient and Carer Involvement

We received patient group submissions from Leukaemia CARE and Bloodwise, both organisations are registered charities. Bloodwise has received 0.9% pharmaceutical company funding in the past two years, including from the submitting company. Leukaemia CARE has received 11.6% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from both organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The economic case presents a cost-utility analysis using a lifetime cohort state-transition model to evaluate gemtuzumab ozogamicin as first line treatment in combination with intensive chemotherapy (daunorubicin plus cytarabine; DA) versus DA alone for patients with previously untreated AML. The economic evaluation focuses on those with favourable, intermediate or unknown cytogenetic profiles.

In the analysis, patients received gemtuzumab ozogamicin as per the licence and clinical data were predominantly taken from the ALFA-0701 study. Patients received one or two induction courses, depending on their initial response to treatment. Following induction therapy patients were assessed as having CR, CRp, or failed induction therapy (i.e. refractory). Salvage therapy could be given, as in the clinical study ALFA-0701.

Response was generally defined as event free survival (sometimes used interchangeably as relapse free survival (RFS) when considering those in whom a response was at least initially shown). Patients who relapse from CR health states and refractory health states could receive haematopoietic stem cell transplant (HSCT) based on the rates from the clinical study. Patients then move to a post-transplant health state. Patients who remain in the CR, CRp or post-HSCT CR or CRp health states without relapsing for a duration of 5 years were considered cured. An excess mortality rate was applied to these patients in the model but they are assumed to experience the same quality of life as the general population.

To extrapolate the data over the model time horizon, survival curves were fitted by treatment arm to RFS and OS data for patients entering CR or CRp. For OS of refractory patients, data were pooled on the basis that gemtuzumab ozogamicin would not affect OS in these patients. Various methods were considered for extrapolation of the data to a lifetime time horizon of 40 years, including mixture cure models (MCM), standard parametric functions and flexible spline functions. The base case method used the MCM approach with a log-normal distribution on the basis of goodness of fit and visual inspection of the survival curves.

Utility data were taken from studies found in a review of the literature conducted for this submission, and were either elicited using the EQ-5D or mapped onto it by the original study

authors. Patients on treatment or receiving a HSCT had utility values of 0.66, patients in CR or CRp health states had a utility value of 0.74, and relapsed or refractory patients had a utility of 0.57. Patients considered to be cured had a utility value of 0.82 based on age-adjusted population norms.

Cost data included medicines costs, disease monitoring and the costs associated with adverse events. Patients receiving a HSCT were assumed to be hospitalised for over a month in an isolation room with ongoing care costs applied up to 2 years post-HSCT.

The base case results and selected sensitivity analysis are shown in Table 3 below.

Table 3. Base case results and selected sensitivity analysis

Analysis	ICER (£)
Base case	10,116
10 year time horizon	18,113
Extend the cure point: 10 years	11,305
Extend the cure point: 20 years	12,583
Remove HSCT from model	17,703
Generalised gamma function used for RFS and OS (CR)	16,352

ICER = incremental cost-effectiveness ratio

Key limitations are:

- There was no significant difference in overall survival in the ALFA-0701 study but the model predicts a material life year gain with gemtuzumab ozogamicin. Although it is acknowledged that the study was not powered to detect a difference in overall survival, the estimated survival gain is large and it is not clear that the model overall survival estimates have been fully tested. Alternative extrapolation assumptions were used in sensitivity analysis and these had some impact on the results; for example when the generalised gamma distribution was used to extrapolate RFS and overall survival for complete remission the ICER increased (see Table 3 above). The company also provided a sensitivity analysis which reduced the time horizon to 10 years and the results are available in Table 3.
- The model assumes patients who have not relapsed after 5 years are considered to be cured and to have a quality of life comparable with the general population, but discussions at SMC suggested this may not be appropriate as there remains a risk of relapse beyond this time point. The company has provided additional sensitivity analysis where the cure assumption was extended to 20 years and the results are available in Table 3 above.

The Committee also considered the benefits of gemtuzumab ozogamicin in the context of the SMC decision modifiers that can be applied and agreed that as gemtuzumab ozogamicin is an 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 modifier, the Committee accepted gemtuzumab ozogamicin for restricted use in NHS Scotland.

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

Additional information: guidelines and protocols

The European LeukemiaNet consensus guidance "Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel" was published in November 2016.[7] Standard intensive induction chemotherapy is recommended to comprise seven days of cytarabine continuous infusion (100 to 200 mg/m^2) and three days of anthracycline (eg daunorubicin 60mg/m^2). Consolidation therapy recommended in the guidance include allogeneic SCT (adverse- or intermediate-risk genetics), or between two and four cycles of intermediate dose cytarabine. The guideline was unable to make firm recommendations for gemtuzumab ozogamicin, citing conflicting outcomes across a range of studies that used different dosing schedules, and noted that its dose and schedule may be critical for the benefit to toxicity ratio.[7]

The European Society for Medical Oncology (ESMO) published guidance "Acute myeloblastic leukaemias in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up" in August 2013.[6] The guidance recommends that "whenever possible AML treatment should be offered in clinical trials and given only in experienced centres offering adequate multidisciplinary infrastructure as well as suitably high case load. Induction chemotherapy should include an anthracycline and cytarabine with the particularly well-known and time-honoured '3+7' regimen…Consolidation therapy in AML is warranted once patients have reached clinical and haematological remission. There is no consensus on a single 'best' post-remission treatment."[6]

The British Society for Haematology last updated its guidelines on management of AML in adults (outside of pregnancy) in 2006; they have been archived.[8]

The guidelines predate the licensing of gemtuzumab ozogamicin.

Additional information: comparators

Gemtuzumab ozogamicin would be given in addition to existing intensive chemotherapy regimens (eg daunorubicin and cytarabine). The cost table below includes schedules used in the ALFA-0701 study and schedules used in the UK based on AML study protocols.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per course (£)
gemtuzumab ozogamicin	**Induction** **3mg/m^2 IV per day (maximum of one 5mg vial)** **days 1, 4 and 7**	**18,900**
	Consolidation **3mg/m^2 IV per day (maximum of one 5mg vial)** **day 1**	**6,300**
daunorubicin cytarabine (ALFA-0701)	Induction daunorubicin 60mg/m^2 IV on days 1 to 3 cytarabine 200mg/m^2 IV on days 1 to 7	1,285
	Consolidation daunorubicin 60mg/m2 IV on day 1 (and day 2 in course 2) cytarabine 1g/m^2 IV twice daily on days 1 to 4	979 to 1,369
daunorubicin cytarabine (AML studies)	Induction Course 1 daunorubicin 60mg/m^2 IV on days 1 to 3 cytarabine 100mg/m^2 IV twice daily on days 1 to 10 Course 2 Daunorubicin 50mg/m^2 IV on days 1 to 3 Cytarabine 100mg/m^2 IV twice daily on days 1 to 8	Course 1 1,334 Course 2 1,106
	Consolidation cytarabine 3g/m^2 IV twice daily on days 1, 3 and 5	1,325

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNFonline, except for gemtuzumab ozogamicin (from dm+d database) on 04 June 2018. Costs calculated using the full cost of vials / ampoules assuming wastage and based on body surface area of 1.8m^2.

Additional information: budget impact

SMC is unable to publish the 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.

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

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This assessment is based on data submitted by the applicant company up to and including 13 July 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*

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.

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.