Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.
1 Guidance

1.1 Ofatumumab is not recommended for the treatment of chronic lymphocytic leukaemia that is refractory to fludarabine and alemtuzumab.

1.2 People currently receiving ofatumumab for the treatment of chronic lymphocytic leukaemia that is refractory to fludarabine and alemtuzumab should have the option to continue treatment until they and their clinician consider it appropriate to stop.
2 The technology

2.1 Ofatumumab (Arzerra, GlaxoSmithKline) is a fully human, high-affinity monoclonal antibody that is targeted against the CD20 cell surface antigen of B-lymphocytes. Ofatumumab has a conditional marketing authorisation for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab. Ofatumumab is delivered by intravenous infusion. The recommended dose is 300 mg of ofatumumab for the first infusion and 2000 mg of ofatumumab for subsequent infusions. The infusion schedule is eight consecutive weekly infusions, followed 4–5 weeks later by four consecutive monthly infusions (that is, every 4 weeks). Patients receiving ofatumumab should be pre-medicated with corticosteroids, analgesics and antihistamines 30 minutes to 2 hours before the infusion. Ofatumumab is not licensed for use in children under 18 years of age.

2.2 The summary of product characteristics (SPC) lists the following adverse effects as being most commonly associated with ofatumumab: infections (especially respiratory tract infections), infusion-related reactions, neutropenia, rash and anaemia. Infusion-related reactions occur most commonly with the first infusion and less frequently with subsequent infusions. Serious adverse events include high-grade (grade 3 or above) neutropenia and high-grade infections. For full details of side effects and contraindications, see the SPC.

2.3 Ofatumumab is currently available in 100 mg (5 ml) vials. The cost of ofatumumab is £182.00 per 100 mg vial, excluding VAT (Monthly Index of Medical Specialities [MIMS], August 2010). The manufacturer of ofatumumab has agreed a patient access scheme with the Department of Health, in which ofatumumab will be made available to the NHS at a discounted price. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.
3 The manufacturer’s submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of ofatumumab and a review of this submission by the Evidence Review Group (ERG; appendix B).

Clinical effectiveness

3.1 The manufacturer’s submission compared ofatumumab with best supportive care. The main source of evidence on clinical effectiveness was the Hx-CD20-406 study. This was a prospective uncontrolled trial that included 154 patients with chronic lymphocytic leukaemia, all of whom received ofatumumab, and 59 of whom had disease that was refractory to both fludarabine and alemtuzumab (that is, double-refractory chronic lymphocytic leukaemia). It also included 79 patients with chronic lymphocytic leukaemia that was refractory to fludarabine but for whom alemtuzumab was unsuitable because of bulky disease, and 16 patients who were not classified into either of these two groups. The evidence reported in the manufacturer’s submission and considered in the appraisal was from the group of patients with double-refractory chronic lymphocytic leukaemia (that is, 59 patients from the total of 154 treated patients). Enrolment began in June 2006 and data were taken from a planned interim analysis with a cut-off date of May 2008. The manufacturer did not provide updated data at the time of the appraisal.

3.2 In the group of 59 patients with double-refractory chronic lymphocytic leukaemia, the median age was 64 years (range 41–86 years), with 7% of patients aged 75 years or over; 75% of patients were men. On average, patients had been diagnosed with chronic lymphocytic leukaemia 6 years before the start of the trial. Patients had received a median of five prior treatments, and 59% of patients had received some form of rituximab regimen previously. The majority of patients at baseline had high-risk chronic lymphocytic leukaemia (that is, Rai stage III or IV and Binet stage C). In relation to the presence of 17p and 11q genetic mutations, which are associated with poorer survival, 29% of patients had a 17p chromosomal deletion and 41% had an 11q chromosomal deletion. Of the 59 patients, 93% received at least eight infusions of ofatumumab and 54% received all 12 infusions. Fifty-three percent of patients who had double-refractory disease went on to receive subsequent treatments after ofatumumab. A wide variety of monotherapy and combination therapies
were given, but only the names of the drugs and the start date were recorded. The dose was not recorded.

3.3 The primary outcome was the objective response rate (ORR; a composite measure that included reduction in tumour size, and improvements in constitutional symptoms, organomegaly and haematological parameters), which was measured 24 weeks after the start of treatment. Ofatumumab was considered to be effective if the ORR was 15% or above. At the interim analysis, the condition of 34 patients with double-refractory chronic lymphocytic leukaemia had responded to ofatumumab treatment, whereas the condition of 25 patients had not responded. This gave an ORR of 58% (99% confidence interval [CI] 40–74%, p < 0.0001) according to an Independent Review Committee evaluation of all patients with double-refractory disease treated with ofatumumab, irrespective of adherence. All responses were partial remission (that is, 58% of patients had a partial remission). Stable disease, defined as not having a complete or partial remission but no disease progression, was noted in a further 31% of patients.

3.4 Pre-specified subgroup analyses of ORR were conducted, although the trial was not powered to detect differences between the subgroups. The 17 patients with double-refractory chronic lymphocytic leukaemia who had a 17p chromosomal deletion, had a lower ORR (41%) than the population with double-refractory disease as a whole (58%). There were also some differences for patients with 12q trisomy or 13q deletion, but the numbers of patients in these subgroups were small (n = 3–7). The manufacturer stated that, otherwise, the ORRs appeared to be similar between subgroups.

3.5 Secondary outcomes included time to onset of response, duration of response, progression-free survival, time to next therapy for chronic lymphocytic leukaemia, overall survival, reduction in tumour size, and safety and pharmacokinetic endpoints. At the time of the interim analysis, there had been 27 deaths (46%). Median overall survival for all patients with double-refractory disease at the time of the interim analysis was 13.7 months (95% CI 9.4 months; upper limit not yet reached at interim analysis). Median overall survival for the subgroup whose condition did not respond to treatment with ofatumumab was estimated to be 8.4 months (95% CI 2.9 to 13.7 months). In the subgroup whose condition responded to treatment, it was too early to estimate median overall survival from the available data at the time of the interim analysis. Median
progression-free survival for all patients with double-refractory disease was 5.7 months (95% CI 4.5 to 8.0 months). For patients whose condition responded to ofatumumab treatment, median progression-free survival was estimated at 8.0 months (95% CI 5.5 to 8.7 months), compared with 4.1 months (95% CI 2.6 to 5.5 months) for patients whose condition did not respond to treatment.

3.6 The most common adverse events judged by the trial investigator to be associated with ofatumumab treatment, which occurred in 61% of patients with double-refractory chronic lymphocytic leukaemia, were infusion-related reactions and infections. The majority of infections were grade 1 or 2. Eighty-six percent of patients with double-refractory disease experienced grade 1 or 2 adverse events, and 64% experienced grade 3 to 5 adverse events. Grade 3 and 4 events were mainly neutropenia and pneumonia. Twelve patients (20%) had drug-related infections of grade 3 or above, 12 patients (20%) had fatal adverse events (grade 5) and 12 patients (20%) withdrew because of adverse events. Six patients (10%) had a non-IgE-mediated anaphylactoid reaction.

3.7 Data on health-related quality of life were not collected in the Hx-CD20-406 study.

3.8 The manufacturer also conducted a systematic review of the literature to identify studies defining the natural history of chronic lymphocytic leukaemia in patients not treated with ofatumumab, and identified two other non-randomised studies (Tam et al. 2007; Dungarwalla et al. 2008). The Tam study was an observational study conducted in the USA. It included 58 patients with chronic lymphocytic leukaemia whose disease was refractory to both fludarabine and alemtuzumab and 41 patients with bulky fludarabine-refractory disease who were treated with a variety of salvage therapies between 1987 and 2006. The Dungarwalla study followed four patients with double-refractory chronic lymphocytic leukaemia and 12 patients with bulky fludarabine-refractory disease who were treated with rituximab and high-dose corticosteroid. The manufacturer did not include data from these studies in the analysis of the clinical effectiveness of ofatumumab. However, the manufacturer drew comparisons with the Tam study in order to estimate expected survival for the group of patients with double-refractory disease when discussing the criteria for life-extending, end-of-life treatments, in relation to safety and to justify the comparators used.
Cost effectiveness

3.9 A systematic review did not identify any relevant published economic evaluations, so the manufacturer developed a new economic model. This three-stage model included the following health states: alive and progression-free; alive and post-progression; and death. All patients entered the model in the progression-free state. An 'area under the curve' or 'partitioned survival' approach was used to estimate mean time to disease progression and mean survival. Data on the effectiveness of treatment were taken from the interim analysis of the Hx-CD20-406 study, which included 59 patients with double-refractory chronic lymphocytic leukaemia (see section 3.1). The estimates of effectiveness associated with ofatumumab treatment were taken from data on all 59 patients, whether or not their condition responded to treatment. Data for the effectiveness of best supportive care were taken from the subgroup of 25 patients whose condition was considered not to have responded to ofatumumab treatment. For the base-case analysis, in order to obtain data on overall survival and progression-free survival for the best supportive care arm, the manufacturer fitted data on time to treatment failure to Weibull curves for patients whose condition did not respond to ofatumumab treatment in the Hx-CD20-406 trial. Estimates of hazard ratios for progression-free survival and overall survival for ofatumumab versus best supportive care were derived from a multivariate Cox proportional hazards regression analysis. These values were then applied to the estimated Weibull survival functions for best supportive care to obtain curves for overall survival and progression-free survival for the ofatumumab arm. The regression analyses included covariates for age, sex, Rai score, Eastern Cooperative Oncology Group (ECOG) status, number of prior therapies and time since diagnosis to obtain an adjusted hazard ratio. A sensitivity analysis was conducted by fitting the Weibull curves for the ofatumumab and best supportive care arms independently.

3.10 The time horizon was 10 years, with a cycle length of 1 day and no half-cycle correction. In line with NICE’s reference case, health effects were measured in quality-adjusted lifeyears (QALYs) and a discount rate of 3.5% was applied to utilities and costs.

3.11 Health-related quality-of-life data were taken from a conference poster published in 2008 (Ferguson et al.). This described the results of a health state preference study that used the time trade-off method with 60 members of the
UK general public to generate utility values relating to health states for patients with chronic lymphocytic leukaemia. The utility values used for progression-free survival and progressive disease were 0.65 and 0.47 respectively, corresponding to two health states described as ‘following second-line treatment’. Final data from a second health state preference study commissioned by the manufacturer were not available at the time of the original submission. However, interim data were provided in response to a request for clarification by the ERG. Costs were based on the NHS and Personal Social Services perspective. Costs for drug acquisition, drug administration, disease management (such as monitoring, imaging, laboratory tests, prophylaxis against infections and transfusions) and adverse events were included.

3.12 The base-case results estimated by the manufacturer were 0.850 QALYs gained with ofatumumab, compared with 0.497 QALYs gained with best supportive care. Costs for ofatumumab in the manufacturer’s model were £13,565 higher than costs for best supportive care (patient access scheme included). The incremental cost-effectiveness ratio (ICER) was £38,421 per QALY gained for ofatumumab compared with best supportive care.

3.13 The manufacturer conducted sensitivity analyses, including one-way deterministic and probabilistic sensitivity analyses. The manufacturer varied the utility values, non-drug costs, mean dose of ofatumumab, curve fits for overall survival and progression-free survival, and whether the effects of 17p and 11q chromosomal deletions were included or excluded in the estimate of effectiveness. In the sensitivity analyses, the manufacturer included other utility values from Ferguson (2008). For progression-free survival, these were 0.777 after first-line treatment and 0.428 after final (third-line) treatment. The utility values for progressive disease were 0.540 after first-line treatment and 0.279 after final (third-line) treatment. The manufacturer also conducted sensitivity analyses using utility values from a general population study (Kind et al. 1999), which gave values of 0.8 for both progression-free survival and progressive disease. With these alternative utility values, the ICERs for ofatumumab compared with best supportive care ranged from £24,635 to £62,654 per QALY gained in the sensitivity analyses. When alternative pharmacy and dispensing costs were used, the ICER was £38,833 per QALY gained. When the estimated overall survival for patients receiving best supportive care was reduced by 50%, the ICER decreased to £27,800 per QALY gained. Including the effects of chromosomal deletions (17p and 11q) as covariates in the Weibull model gave
an ICER of £50,322 per QALY gained. A probabilistic sensitivity analysis using the base-case ICER with the discounted price (patient access scheme) gave a 28% chance of ofatumumab being cost effective at a willingness-to-pay threshold of £30,000 per QALY gained.

Evidence Review Group comments

3.14 The main issue highlighted by the ERG about the evidence on the clinical effectiveness of ofatumumab was the absence of robust evidence from randomised controlled trials. The ERG was concerned that it could not accurately assess the impact of bias on the outcomes, including adverse events. The ERG noted the limitations of the evidence, including that the outcome data were from a planned interim analysis and no recent data were available, and that the population presented in the analysis comprised only 59 patients. Also, the study lacked health-related quality-of-life data. The ERG noted differences between the subgroups of patients whose condition did or did not respond to ofatumumab with regard to clinical characteristics at baseline. The ERG also noted that a regression analysis that took into account patients with 17p and 11q chromosomal deletions could have been included in the base case. The ERG otherwise considered that the manufacturer had searched the literature appropriately, although it expressed concern that the manufacturer chose to exclude the Tam study that was identified by the literature search from the analysis of the clinical effectiveness of ofatumumab versus best supportive care and from the economic model.

3.15 The ERG considered that the overall modelling approach of the manufacturer was reasonable considering the paucity of clinical evidence available. The ERG did not find any logical errors in the economic model, but did identify areas of weakness and uncertainty. The main concern was the manufacturer’s use of data from the subgroup of patients whose condition did not respond to treatment with ofatumumab from the Hx-CD20-406 trial to model the effectiveness associated with best supportive care and the use of data from all patients treated in the double-refractory group to model the effectiveness associated with ofatumumab. It was not clear how having data from patients whose condition did not respond to treatment in both arms of the analysis (best supportive care subgroup and total double-refractory group) would bias the estimation of the treatment effect of ofatumumab. The ERG also noted that the manufacturer did not use any other data, such as controls from observational
studies or from randomised trials of other agents, to model the best supportive care arm. Furthermore, the ERG noted that the utility values were taken from a conference poster (Ferguson 2008) describing a health state preference study, and reflected a health state after second-line treatment rather than after final (third-line) treatment. The ERG felt that the utility values after final (third-line) treatment were more appropriate than the values after second-line treatment, because patients in the pivotal study had received a median of five prior treatments. In addition, the ERG highlighted that there was limited information available about the health states described in the poster and these health states had been formulated using information from the literature, clinical guidelines and specialist nurses and physicians, rather than from patients. The ERG was also concerned by the omission of the effects of 17p and 11q chromosomal deletions as factors in the Cox proportional hazards models for overall survival and progression-free survival, because there was existing evidence that the presence of these deletions is associated with decreased survival. In addition, the ERG noted that 53% of patients with double-refractory disease received subsequent treatments after ofatumumab, but the additional costs of these treatments were not included in the model.

3.16 The ERG presented exploratory analyses that (i) included the effects of chromosomal deletions (17p and 11q) in the multivariate Cox proportional hazards regressions of overall survival and progression-free survival; (ii) used lower utility values corresponding to a health state after final (third-line) treatment; and (iii) included the costs of subsequent drug treatment for patients with progressive disease. The ICER for ofatumumab compared with best supportive care when the measure of effectiveness accounted for the effects of chromosomal deletions 17p and 11q (as well as age, sex, Rai score, ECOG status, number of prior therapies and time since diagnosis) in the Cox regressions was £50,300 per QALY gained. The ICER when alternative utility values of 0.428 and 0.279, representing progression-free and progressive disease health states respectively following final (third-line) treatment, were used instead of values of 0.650 and 0.470 for progression-free survival and progressive disease respectively following second-line treatment, increased the ICER to slightly less than £62,700 per QALY (‘slightly less than’ reflected the prediction of the ERG that the utility value for patients on ofatumumab would be slightly higher than that for patients on best supportive care). The inclusion of costs of subsequent drugs for patients with progressive disease after treatment with ofatumumab increased the ICER above the base-case figure of £38,400 per QALY gained by
several thousand pounds – it was not possible for the ERG to provide a more precise estimate because of a lack of information on drug dosages. The cumulative impact of these three changes resulted in an alternative estimated ICER for ofatumumab compared with best supportive care of thousands of pounds more than £81,500 per QALY gained when using the cost of ofatumumab proposed in the patient access scheme, compared with £38,400 per QALY gained in the manufacturer's base case.

3.17 The ERG conducted sensitivity analyses that included the interim data from the health state preference study commissioned by the manufacturer. The final data from this study, provided by the manufacturer in response to consultation on the appraisal consultation document, were identical to the interim data. This study used the time trade-off method with 110 representative members of the UK adult population to obtain utility values for descriptions of progression-free and progressive disease health states associated with double-refractory chronic lymphocytic leukaemia. The descriptions of the health states were developed from information from the literature, patient organisation websites and specialist clinicians. The ERG applied the reported utility value for progressive disease of 0.214 to both treatment arms. The ERG used the utility value of 0.394, described as that for progression-free survival for patients whose disease had not responded to ofatumumab treatment, for patients in the best supportive care arm. The ERG then calculated a utility value of 0.555 for progression-free survival for patients in the ofatumumab arm. This was done by averaging the values for patients whose disease had responded to ofatumumab treatment (0.671) and patients whose disease had not responded (0.394), weighted by the proportion of patients in the single-arm trial whose disease had responded (that is, 58%). When the ERG included these values in sensitivity analyses using the manufacturer’s model, the manufacturer’s base-case ICER of £38,400 per QALY gained increased to £52,100 per QALY gained. The ERG’s proposed alternative ICER (including the three changes described in section 3.16) decreased from more than £81,500 to more than £60,500 per QALY gained when the alternative utility values were used.

3.18 Full details of all the evidence are in the manufacturer's submission and the ERG report.
4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of ofatumumab, having considered evidence on the nature of chronic lymphocytic leukaemia and the value placed on the benefits of ofatumumab by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.2 The Committee considered the views of the clinical specialists and patient expert on the clinical need and available treatment options for people with chronic lymphocytic leukaemia that is refractory to fludarabine and alemtuzumab. The Committee heard from the clinical specialists that these patients would have received most available treatments and that best supportive care would probably be the main treatment option. The clinical specialists confirmed that patients may have already received rituximab (as had 59% of patients with double-refractory disease in the Hx-CD20-406 trial) and that treating patients in this group again with rituximab regimens or other treatments may result in a limited response. The clinical specialists and patient expert highlighted that the prognosis of people with refractory chronic lymphocytic leukaemia depends on the availability of further treatments and that prognosis with best supportive care alone is poor. The clinical specialists stated that it was important to have additional treatment options, such as ofatumumab, later in the treatment pathway. The Committee heard from the clinical specialists that alemtuzumab has limited use in UK clinical practice, in part because of its cost and tolerability profile. Consequently, the Committee accepted the number of people with double-refractory chronic lymphocytic leukaemia who are eligible for treatment with ofatumumab according to the marketing authorisation is small.

4.3 The Committee then heard from the clinical specialists and patient expert that ofatumumab appeared to be effective in early-phase trials. The clinical specialists acknowledged that ofatumumab, like rituximab, targets CD20, but considered that it may offer a slightly different mechanism of action because it targets a different epitope. The Committee also heard that ofatumumab is given at a higher dose than existing treatments, which could explain any potential superior clinical effectiveness. This also indicates that it may be better
tolerated, particularly by older patients or those with a poorer prognosis. The Committee concluded from the discussions with the clinical specialists and patient expert that patients with double-refractory chronic lymphocytic leukaemia have a particularly poor prognosis and limited treatment options.

4.4 The Committee discussed the evidence for the clinical effectiveness of ofatumumab. The Committee noted that all of the evidence came from a subgroup from an interim analysis of a non-randomised, uncontrolled (single-arm) study of ofatumumab. The Committee heard from the clinical specialists about the difficulties of conducting randomised trials in patients with double-refractory chronic lymphocytic leukaemia because of the lack of an appropriate comparator and the small size of the population, and because the manufacturer considered such studies to be unethical and difficult to recruit to. The Committee heard from a clinical specialist that methylprednisolone could have been considered as a potential comparator in a trial for patients with double-refractory disease. The Committee further discussed the potential biases associated with the study design. The Committee was aware that all patients in the Hx-CD20-406 trial received ofatumumab, and agreed that it was therefore difficult to ascribe any clinical response to ofatumumab. In the absence of data on patients not taking ofatumumab, the Committee was concerned that the patients whose condition responded to ofatumumab may have been fundamentally different in a way that influenced their prognosis relative to those whose condition did not respond. The Committee also voiced concerns about the small numbers of patients in this analysis. It heard from the ERG that the biases caused by these various aspects of the study design could have led to either an overestimation or an underestimation of the effectiveness of ofatumumab. The Committee recognised the difficulty of conducting randomised controlled trials in small populations of patients with limited life expectancy, as highlighted by the clinical specialists. However, the Committee concluded that such difficulties could have been addressed more effectively than they had been in the manufacturer’s submission.

4.5 The Committee then considered the way the manufacturer explored the effectiveness of best supportive care and noted that the estimated overall survival was approximately 8 months with best supportive care in the manufacturer’s submission, based on the subgroup of people whose disease did not respond to ofatumumab. The Committee discussed the potential for using data from historical controls, for example from retrospective observational
studies (such as the study by Tam identified by the manufacturer). The manufacturer estimated overall survival with best supportive care in the Tam study to be 8.4 months. The manufacturer stated that the Tam study was not formally included in the submission because of the lack of data on progression-free survival, and because the study included a heterogeneous population and treatments that are not considered to be standard care in the UK. The Committee noted that the manufacturer highlighted that the Tam study should only be used to give context to the clinical data and that the study emphasised that people with chronic lymphocytic leukaemia have a poor prognosis. The Committee acknowledged that the Tam study had limitations, such as the fact that it included data from 1987 to 2006 and that standard care and survival were likely to have improved over this time. The Committee considered that the absence of any analysis in the manufacturer's submission using the data from the Tam study meant that it was not able to formally evaluate the strengths and limitations of the Tam study data. However, the Committee noted that the survival data of 8–9 months was broadly similar to those already presented in the manufacturer's submission, and therefore considered that it was unlikely that any additional analyses that included these data would change the conclusions based on the current evidence.

4.6 The Committee heard from the clinical specialists that it may be possible to obtain relevant survival estimates from alternative sources. The clinical specialists stated that studies of alemtuzumab may contain data from ofatumumab-naive patients with double-refractory disease that could be used for comparisons with the effectiveness of ofatumumab. The Committee heard from the manufacturer that this approach had not been considered at the time of the original submission. The Committee heard from the manufacturer that a trial of alemtuzumab for patients whose disease had not responded to fludarabine had been identified, and the results for patients whose disease failed to respond to alemtuzumab could be used to estimate the survival of patients receiving best supportive care. The Committee acknowledged that the manufacturer was currently investigating this source of data, but that full results were not available for the second Committee meeting. The Committee heard that the manufacturer had extracted survival data from Kaplan–Meier curves presented in a publication of the trial. For the patients whose disease had failed to respond to fludarabine and then alemtuzumab, median overall survival was approximately 8–9 months for patients with double-refractory disease. The manufacturer could not provide details of any further treatments that these
patients in the alemtuzumab trial may have received. The Committee noted that these analyses provided results similar to those of the Tam study as well as those for patients whose disease had not responded in the pivotal ofatumumab study (Hx-CD20-406). The Committee considered that the additional analysis would still be associated with uncertainty but could provide a more robust estimate of survival with best supportive care than was currently available. However, the Committee concluded that, as the survival data were similar to those already presented by the manufacturer in the original submission, it was unlikely that the additional data would change its conclusions based on the existing evidence.

4.7 The Committee also noted that the manufacturer had not provided more recent data from the Hx-CD20-406 study (the interim analysis was from May 2008, with no further data expected before 2011). The Committee heard from the manufacturer that this interim analysis was planned in the study protocol and that an unplanned analysis would not be possible, in accordance with best statistical practice in clinical trials, which discourages unplanned interim analyses. The Committee therefore concluded that there were insufficient data on overall survival to provide valid estimates of the effectiveness of ofatumumab.

4.8 The Committee then heard from the clinical specialists that the size of the response to ofatumumab in the Hx-CD20-406 study was much greater than that following treatment with other monotherapies in this patient population. The clinical specialists stated that ORRs reported for other treatments (excluding alemtuzumab) were generally poor (15% or lower per course of treatment). The clinical specialists found the magnitude of the response with ofatumumab surprising, but plausible. The Committee heard from the manufacturer that regulatory agencies had acknowledged this high response rate, by granting early or accelerated marketing authorisation for ofatumumab. The Committee was aware that this marketing authorisation was classified as conditional, as the European Medicines Agency requires the manufacturer to perform an observational study of ofatumumab for this indication to provide further data on the efficacy and safety of ofatumumab. The clinical specialists added that patients who did not fulfil the criteria for an objective response in clinical trials but who had stable disease may still benefit from treatment. The Committee noted that there were no data on median overall survival available for patients whose condition responded to treatment because the data were
Immature. The Committee agreed that, although it was likely that ofatumumab is clinically effective based on the observed ORRs, it was not possible to estimate the size of the clinical effect with certainty because of the absence of robust and comparative evidence and the immaturity of the data on overall survival.

4.9 The Committee heard from the clinical specialists about the adverse events associated with ofatumumab. It noted that most adverse events were associated with the initial infusion, and that these were manageable and did not tend to recur. The Committee acknowledged that all patients in the Hx-CD20-406 study were given ofatumumab and so it was uncertain whether some adverse events were caused by the treatment or the disease itself. In particular, the clinical specialists stated that infections are a common consequence of chronic lymphocytic leukaemia. The Committee noted that six patients with double-refractory disease in the trial experienced anaphylactoid events, although the clinical specialists stated that such a high proportion of patients having this reaction had not been their experience. The Committee concluded that ofatumumab may be associated with adverse events, but the extent and impact of these adverse events was uncertain owing to a lack of robust evidence and the lack of a group of patients who did not receive ofatumumab in the trial.

4.10 The Committee concluded that, based on expert evidence, it was plausible that ofatumumab may offer clinical benefits to patients, but that it was not possible to determine the magnitude of the effect from the evidence presented. The Committee noted that although ofatumumab has a slightly different mechanism of action to rituximab, there was insufficient robust evidence available for it to conclude that this technology was innovative and would make a significant and substantial impact on health-related benefits in the treatment of chronic lymphocytic leukaemia that is refractory to fludarabine and alemtuzumab.

**Cost effectiveness**

4.11 The Committee discussed the evidence for the cost effectiveness of ofatumumab that was submitted by the manufacturer. It noted the base-case ICER provided by the manufacturer of £38,400 per QALY gained for ofatumumab compared with best supportive care. The Committee was aware that the manufacturer's economic model incorporated a patient access scheme.
in which ofatumumab would be made available to the NHS at a discounted price. The Committee noted that the scheme had been approved by the Department of Health and considered that all ICERs incorporating the patient access scheme were appropriate for consideration.

4.12 The Committee discussed the estimates of treatment effect that were used in the model. The Committee was aware that the manufacturer had used data from all patients with double-refractory disease in the Hx-CD20-406 trial to estimate the effectiveness of ofatumumab, and data from patients whose condition did not respond to ofatumumab treatment to estimate the effectiveness of best supportive care. The Committee noted that the manufacturer considered this a conservative approach because people modelled as receiving best supportive care actually had received active treatment which could have had some effect, but noted that the method did not control for other likely statistical correlations. The Committee was concerned about the scientific basis of this method. Because all patients were treated with ofatumumab, the Committee did not consider that using the data from the patients whose condition did not respond to treatment to model best supportive care was comparable to comparing ofatumumab with placebo. The Committee noted that since data for the ofatumumab arm were from all patients, these included data from patients who were also in the arm modelled as best supportive care. This may have biased the estimates of treatment effect, but the direction and magnitude of any effect were uncertain. However, the Committee considered that in a placebo-controlled trial there would be some people who would experience a response to placebo (that is, a 'placebo effect'). Therefore as the best supportive care arm was modelled using data from patients whose disease had not responded to active treatment, this could have underestimated the survival that may have been observed in the control arm of a placebo-controlled trial, where some placebo effect would have been expected. Also, the Committee noted its earlier conclusion that those in the non-responder arm may have had a condition with poorer prognosis (section 4.4). The Committee concluded that there was a lack of robust evidence demonstrating the clinical effectiveness of ofatumumab, and that this in turn increased the uncertainty in the ICERs.

4.13 The Committee then discussed the immature data from the Hx-CD20-406 study on overall survival for patients whose condition responded to ofatumumab treatment, and whether extrapolation beyond the trial duration
further increased the uncertainty surrounding the estimates of overall survival and progression-free survival. The Committee discussed whether the manufacturer had chosen the most appropriate survival curves for extrapolation. The Committee heard from the ERG that both approaches to extrapolation (that is fitting the survival curves independently to the data and fitting the survival curves by applying a hazard ratio) resulted in curves that were good fits to the empirical data. However, the Committee acknowledged that the curves that were fitted independently did not account for any confounding factors, as well as the possibility that the hazard ratio associated with achieving an overall response might be attenuated when taking into account the differing baseline characteristics in the subgroups of patients whose condition did, or did not, respond to treatment. The Committee discussed the exclusion of the effects of chromosomal deletions from the proportional hazards model for progression-free survival and overall survival. The clinical specialists informed the Committee that the fact that chromosomal deletions decrease the probability of a response to treatment was less important in this population than in patients with earlier-stage disease. However, the Committee noted that there was an imbalance in the number of patients with chromosomal deletions in the subgroups whose condition did and did not respond to treatment. It also heard from the manufacturer that when these chromosomal deletions were included in regression analysis, the estimated effect of ofatumumab decreased. The Committee agreed that the chromosomal deletions should have been included in the regression analysis and in the subsequent modelling of the ofatumumab survival curves. The Committee noted that the inclusion of these chromosomal deletions increased the manufacturer's base-case ICER from £38,400 to £50,300 per QALY gained.

4.14 The Committee discussed the expected duration of treatment with ofatumumab. It heard from the clinical specialists that in standard clinical practice patients would be monitored and that treatment would be stopped after 8 weeks if there was no response. These patients would then be offered best supportive care, or novel agents in clinical trials. However, the clinical specialists also confirmed that patients whose condition is defined in a clinical trial as not responding but who have stable disease may still benefit from treatment in clinical practice. The Committee noted that treatment had continued in the Hx-CD20-406 study beyond 8 weeks and that no stopping rule had been applied for patients whose condition had not responded to ofatumumab treatment by this time.
4.15 The Committee considered the impact of including the costs of subsequent treatment for patients with progressive disease in the economic model, since these costs were excluded from the submitted base-case model. The Committee noted that in the clinical trial, approximately half of the patients received subsequent treatments after disease progression, and that the costs of these additional treatments had not been included in the manufacturer’s economic model. It considered that it was plausible that the additional treatments given during disease progression could result in improvements in overall survival, and therefore agreed that these additional costs should also be included in the economic model. The Committee noted comments from the ERG that the inclusion of these costs would increase the ICER (by thousands of pounds per QALY gained), but could not be specified exactly as the manufacturer did not provide information on subsequent treatments. Based on the information from the clinical specialists, the Committee agreed that although the additional costs were not likely to be as high as those suggested by the ERG, including these costs would increase the ICERs.

4.16 The Committee considered the selection of utility values and their potential impact on the estimate of the cost effectiveness of ofatumumab in the manufacturer’s economic model. The Committee noted that health-related quality of life had not been collected in the pivotal study of ofatumumab. The Committee was concerned that the utilities used in the manufacturer’s original submission had been obtained from a conference poster which, although published, provided minimal details about the methods used. In addition, the Committee noted that these utility values were associated with health states after second-line therapy and agreed that utility values associated with third-line therapy would have been more appropriate. Data from a second report describing a health state preference study commissioned by the manufacturer was also considered by the Committee. The Committee acknowledged that there was uncertainty surrounding all of the utility values because the health state descriptions in both studies were derived from the literature, other publicly available information and specialist nurses and physicians rather than directly from patients. In addition, the Committee was uncertain whether including utility values representing health states defined by disease response and non-response was appropriate, because response was defined in the trial by clinical factors such as tumour size, constitutional symptoms, organomegaly and haematology rather than factors that are meaningful to patients and have a direct impact on health-related quality of life. The Committee also discussed the
impact of adverse events and noted that the extent to which this had been incorporated in the selected utility values was uncertain. The Committee agreed that the utility values used in the manufacturer's base case were inappropriate and that the lower utility values reflecting the health state after a final (third-line) treatment, or the utility values from the manufacturer's commissioned study, although associated with uncertainty, were more appropriate. The Committee noted that including the final (third-line) values from the poster or the values from the commissioned study increased the ICERs. Therefore, the most plausible ICERs, including costs associated with progressive disease and the impact of chromosomal deletions, increased from more than £50,300 per QALY gained to more than £81,500 per QALY gained when using the utility values after final (third-line) treatment, and to more than £60,500 per QALY gained when using the utility values from the commissioned study.

4.17 This appraisal was based on the analysis of a subgroup from the Hx-CD20-406 study, and the expected population eligible for treatment with ofatumumab is small. The Committee did not identify any other specific groups of people for whom the technology was considered particularly clinically or cost effective.

4.18 After consultation on the appraisal consultation document, the Committee noted that the manufacturer commented that because this appraisal relates to a small group of patients, the overall budget impact of recommending ofatumumab would be low. However, the Committee was aware that, under NICE methods of technology appraisal, the potential overall budget impact of a new technology does not influence the Committee's decision. The Committee also noted that NICE had not received direction from the Department of Health that technologies for rare conditions should be appraised differently from any other technologies.

4.19 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.

The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case economic modelling are plausible, objective and robust.

4.20 The Committee considered whether ofatumumab for the treatment of refractory chronic lymphocytic leukaemia fulfilled the criteria for consideration as a life-extending, end-of-life treatment. The Committee considered the evidence provided in the manufacturer’s submission that expected survival in this population was less than 24 months, and was potentially as low as 8 months. This was similar to data from the historical Tam study (9 months) and the provisional estimate from the alemtuzumab trial for the double refractory patient group (8–9 months). The Committee was aware that the population was small, noting the manufacturer’s estimates of 15 to 39 eligible patients per year. The Committee acknowledged that the manufacturer’s model estimated an extension of life of more than 5 months compared with best supportive care, but felt that this might not reflect an unbiased or robust estimate of extension to life for patients who receive ofatumumab compared with those who do not because of the modelling approach. In addition, the Committee noted that because of the non-comparative evidence base, it was not possible to infer what the extension to life may be from the estimates of progression-free survival. Therefore the Committee considered that under a strict interpretation of the end-of-life criteria, that the evidence presented about extension to life was not sufficiently robust.

4.21 The Committee considered whether the additional analyses being investigated by the manufacturer would be likely to improve the robustness of the estimates of extension to life, and whether the economic modelling would be more plausible, objective and robust. The Committee noted that there would be continuing uncertainty around the estimates of survival and that a number of assumptions would have to be made for incorporation in the economic model. However, the Committee considered that the additional analyses may provide slightly more robust estimates of extension to life, and that it was possible that the criteria for considering ofatumumab as a life-extending, end-of-life treatment might therefore be fulfilled. In light of this, the Committee discussed
whether the additional analyses proposed by the manufacturer might change its conclusions. The Committee noted that the estimates of survival obtained from the preliminary additional analyses were similar to those already used in the economic modelling, and so it was unlikely that the estimates of cost-effectiveness would change from those already considered. The Committee concluded that the most plausible ICER would still be in a range between more than £60,500 and more than £81,500 per QALY gained. The Committee therefore considered that the magnitude of the additional weight that would need to be assigned to the original QALY benefits for this patient group for the ICER of ofatumumab to fall within the required threshold range would be too great. Therefore the Committee concluded that ofatumumab for the treatment of chronic lymphocytic leukaemia that is refractory to fludarabine and alemtuzumab could not be recommended as a cost-effective use of NHS resources.

**Summary of the Appraisal Committee's key conclusions**

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<tr>
<th>TA202 (STA)</th>
<th>Appraisal title:</th>
<th>Section</th>
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<tbody>
<tr>
<td>Key conclusion</td>
<td>The Committee concluded that the most plausible ICER would be between more than £60,500 and more than £81,500 per QALY gained. The Committee concluded that the criteria for consideration as a life-extending, end-of-life treatment were not fulfilled when interpreted strictly, and that even if the robustness of the survival estimates could be improved, it was unlikely that the estimates of cost-effectiveness would change from those already considered and that the magnitude of the additional weight that would need to be assigned to the original QALY benefits for this patient group for the ICER of ofatumumab to fall within the required threshold range would be too great. Therefore the Committee concluded that ofatumumab for the treatment of chronic lymphocytic leukaemia that is refractory to fludarabine and alemtuzumab could not be recommended as a cost-effective use of NHS resources.</td>
<td>4.20 and 4.21</td>
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</table>

**Current practice**
### Clinical need of patients including the availability of alternative treatments

The Committee concluded that patients with double-refractory chronic lymphocytic leukaemia have a particularly poor prognosis and limited treatment options.

### The technology

#### Proposed benefits of the technology

The Committee noted that although ofatumumab has a slightly different mechanism of action to rituximab, there was insufficient robust evidence available for it to conclude that this technology was innovative and would make a significant and substantial impact on health-related benefits in the treatment of chronic lymphocytic leukaemia that is refractory to fludarabine and alemtuzumab.

#### How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits

Ofatumumab has a conditional marketing authorisation ‘for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab’.

The clinical specialists stated that it was important to have additional treatment options, such as ofatumumab, later in the treatment pathway.

#### What is the position of the treatment in the pathway of care for the condition

The most common adverse events associated with ofatumumab treatment, which occurred in 61% of patients with double-refractory chronic lymphocytic leukaemia, were infusion-related reactions and infections.

The Committee concluded that ofatumumab may be associated with adverse events, but the extent and impact of these adverse events was uncertain owing to a lack of robust evidence and the lack of a group of patients who did not receive ofatumumab in the trial.
### Evidence for clinical effectiveness

| Availability, nature and quality of evidence | The Committee noted that there were no data on median overall survival available for patients whose condition responded to treatment because the data were immature. The Committee agreed that, although it was likely that ofatumumab is clinically effective based on the observed ORRs, it was not possible to estimate the size of the clinical effect with certainty because of the absence of robust and comparative evidence and the immaturity of the data on overall survival. The Committee concluded that, based on expert evidence, it was plausible that ofatumumab may offer clinical benefits to patients, but that it was not possible to determine the magnitude of the effect from the evidence presented. | 4.8 and 4.10 |

| Relevance to general clinical practice in the NHS | No specific issues were discussed. | N/A |

<p>| Uncertainties generated by the evidence | The Committee noted that there were no data on median overall survival available for patients whose condition responded to treatment because the data were immature. The Committee agreed that, although it was likely that ofatumumab is clinically effective based on the observed ORRs, it was not possible to estimate the size of the clinical effect with certainty because of the absence of robust and comparative evidence and the immaturity of the data on overall survival. The Committee concluded that, based on expert evidence, it was plausible that ofatumumab may offer clinical benefits to patients, but that it was not possible to determine the magnitude of the effect from the evidence presented. | 4.8 |</p>
<table>
<thead>
<tr>
<th>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness</th>
<th>The Committee did not identify any specific subgroups of people for whom the technology was considered particularly clinically effective.</th>
<th>4.18</th>
</tr>
</thead>
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<tr>
<td>Estimate of the size of the clinical effectiveness including strength of supporting evidence</td>
<td>The Committee concluded that, based on expert evidence, it was plausible that ofatumumab may offer clinical benefits to patients, but that it was not possible to determine the magnitude of the effect from the evidence presented.</td>
<td>4.8</td>
</tr>
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</table>

### Evidence for cost effectiveness

| Availability and nature of evidence | The manufacturer developed an economic model using data from the planned interim analysis of the Hx-CD20-406 study. Data on the effectiveness of ofatumumab treatment were taken from all 59 patients with double-refractory chronic lymphocytic leukaemia who were treated with ofatumumab. Data for the effectiveness of best supportive care were taken from the subgroup of 25 patients whose condition was considered not to have responded to ofatumumab treatment. | 3.9 |
### Uncertainties around and plausibility of assumptions and inputs in the economic model

The Committee noted that since data for the ofatumumab arm were from all patients, these included data from patients who were also in the best supportive care arm. This may have biased the estimates of treatment effect, but the direction and magnitude of any effect were uncertain.

The Committee considered that in a placebo-controlled trial there would be some people who would experience a response to placebo (that is, a 'placebo effect'). Therefore as the best supportive care arm was modelled using data from patients whose disease had not responded to active treatment, this could have underestimated the survival that may have been observed in the control arm of a placebo-controlled trial. Also, the Committee noted that those in the non-responder arm may have had a condition with poorer prognosis.

The Committee concluded that there was a lack of robust evidence demonstrating the clinical effectiveness of ofatumumab, and that this in turn increased the uncertainty in the ICERs.

### Incorporation of health-related quality of life benefits and utility values

The Committee agreed that the utility values used in the manufacturer's base case were inappropriate and that the lower utility values reflecting the health state after a final (third-line) treatment, or the utility values from the manufacturer's commissioned study, although associated with uncertainty, were more appropriate. The Committee noted that including the final (third-line) values from the poster or the values from the commissioned study increased the ICERs. The most plausible ICERs, including costs associated with progressive disease and the impact of chromosomal deletions, increased from more than £50,300 per QALY gained to more than £81,500 per QALY gained when using the utility values after final (third-line) treatment, and to more than £60,500 per QALY gained when using the utility values from the commissioned study.

No potential health-related benefits were identified that were not included in the economic model.
<table>
<thead>
<tr>
<th>Are there specific groups of people for whom the technology is particularly cost-effective?</th>
<th>The Committee did not identify any specific groups of people for whom the technology was considered particularly cost effective.</th>
<th>4.18</th>
</tr>
</thead>
<tbody>
<tr>
<td>What are the key drivers of cost effectiveness?</td>
<td>The Committee agreed that the chromosomal deletions should have been included in the regression analysis and in the subsequent modelling of the ofatumumab survival curves. The Committee noted that the inclusion of these chromosomal deletions increased the manufacturer's base-case ICER from £38,400 to £50,300 per QALY gained. The Committee noted comments from the ERG that the inclusion of these costs would increase the ICER (by thousands of pounds per QALY gained), but could not be specified exactly as the manufacturer did not provide information on subsequent treatments. Based on the information from the clinical specialists, the Committee agreed that although the additional costs were not likely to be as high as those suggested by the ERG, including these costs would increase the ICERS. The Committee noted that including the final (third-line) values from the poster or the values from the commissioned study increased the ICERS. The most plausible ICERS, including costs associated with progressive disease and the impact of chromosomal deletions, increased from more than £50,300 per QALY gained to more than £81,500 per QALY gained when using the utility values after final (third-line) treatment, and to more than £60,500 per QALY gained when using the utility values from the commissioned study.</td>
<td>4.13 4.15 4.16</td>
</tr>
</tbody>
</table>
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<table>
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<tr>
<th>Additional factors taken into account</th>
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<tbody>
<tr>
<td><strong>Patient Access Schemes (PPRS)</strong></td>
</tr>
<tr>
<td>The Committee noted that a patient access scheme, in which ofatumumab would be made available to the NHS at a discounted price, had been approved by the Department of Health. Therefore the Committee considered that all ICERs incorporating the patient access scheme were appropriate for consideration.</td>
</tr>
</tbody>
</table>

| **End-of-life considerations**       |
| The Committee concluded that ofatumumab for the treatment of refractory chronic lymphocytic leukaemia met the criteria of a short life expectancy and a small patient population, but because the evidence for the extension to life was not sufficiently robust, the criteria for consideration as a life-extending, end-of-life treatment were not fulfilled when interpreted strictly. The Committee considered whether the additional analyses being investigated by the manufacturer could improve the robustness of the estimates of extension to life, and noted that the estimates of survival obtained from the preliminary additional analyses were similar to those already used in the economic modelling. It therefore concluded that it was unlikely that the estimates of cost-effectiveness would change from those already considered and that the magnitude of the QALY benefits for the ICER of ofatumumab to fall within the required threshold range would be too great. |

| **Equalities considerations, social value judgements** |
| No equality or diversity issues relating to population groups protected by equality legislation were highlighted when the scope for this appraisal was developed, or during the appraisal. |

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5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below).

- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.
6 Related NICE guidance


7 Review of guidance

7.1 The guidance on this technology will be considered for review in September 2013.

Andrew Dillon
Chief Executive
October 2010
Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between the Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)
Consultant Physician, Addenbrooke's Hospital

Professor Keith Abrams
Professor of Medical Statistics, University of Leicester

Dr Ray Armstrong
Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson
Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Dr Peter Barry
Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Dr Michael Boscoe
Consultant Cardiothoracic Anaesthetist, Royal Brompton and Harefield NHS Foundation Trust
Professor John Cairns
Professor of Health Economics, Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Mark Chakravarty
External Relations Director - Pharmaceuticals & Personal Health, Oral Care Europe

Sally Gooch
Independent Nursing and Healthcare Consultant

Eleanor Grey
Lay member

Sanjay Gupta
YPD Service Case Manager, Southwark Health and Social Care, Southwark PCT

Dr Rosa Legood
Lecturer, London School of Hygiene and Tropical Medicine

Terence Lewis
Lay member

Dr Rubin Minhas
General Practitioner and Clinical Director, BMJ Evidence Centre

Dr Sanjeev Patel
Consultant Physician & Senior Lecturer in Rheumatology, St Helier University Hospital

Philip Pugh
Strategic Development Lead for Healthcare Associated Infection and Antimicrobial Resistance, Health Protection Agency

Dr John Rodriguez
Assistant Director of Public Health, NHS Eastern and Coastal Kent

Dr Florian Alexander Ruths
Consultant Psychiatrist & Cognitive Therapist, Maudsley Hospital, London
Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab (TA202)

Navin Sewak
Primary Care Pharmacist, NHS Hammersmith and Fulham

Dr Lindsay Smith
General Practitioner, East Somerset Research Consortium

Roderick Smith
Finance Director, West Kent Primary Care Trust

Cliff Snelling
Lay member

Professor Ken Stein (Vice Chair)
Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens
Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Dr Rod Taylor
Associate Professor in Health Services Research, Peninsula Medical School, Universities of Exeter and Plymouth

Nathalie Verin
Health Economics Manager, Boston Scientific UK and Ireland

Dr Colin Watts
Consultant Neurosurgeon, Addenbrooke's Hospital

Tom Wilson
Director of Contracting & Performance, NHS Tameside & Glossop

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.
Appendix B: Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Peninsula Technology Assessment Group (PenTAG), Peninsula Medical School, University of Exeter:

- Hoyle M, Crathorne L, Moxham T, et al., Ofatumumab (Arzerra®) for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab: a critique of the submission from GSK, April 2010

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I) Manufacturer/sponsor:

- GlaxoSmithKline

II) Professional/specialist and patient/carer groups:

- British Society for Haematology
- Cancer Research UK
- Chronic Lymphocytic Leukaemia Support Association (CLLSA)
- Macmillan Cancer Support
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians, Medical Oncology Joint Special Committee
- Royal Pharmaceutical Society
- South Asian Health Foundation
- United Kingdom Chronic Lymphocytic Leukaemia Forum
III) Other consultees:

- Department of Health
- Welsh Assembly Government

IV) Commentator organisations (did not provide written evidence and without the right of appeal):

- Cephalon
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Leukaemia & Lymphoma Research
- Medac UK
- NHS Quality Improvement Scotland
- Pfizer
- Roche Products

C. The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on ofatumumab by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Peter Hillmen, Consultant Haematologist, nominated by the British Society for Haematology/Royal College of Pathologists – clinical specialist
- Professor Donald Milligan, Consultant Haematologist, nominated by the NCRI/RCP/RCR/ACP/JCCO – clinical specialist
- Professor Andrew Pettitt, Professor of Haematology, nominated by the UK CLL Forum – clinical specialist
- Jane Barnard, nominated by the Chronic Lymphocytic Leukaemia Support Association – patient expert
D. Representatives from the following manufacturer attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- GlaxoSmithKline
Changes after publication

February 2014: minor maintenance

March 2012: minor maintenance
About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE single technology appraisal process.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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