NICE National Institute for Health and Care Excellence

NICE guidance

Idelalisib for treating chronic lymphocytic leukaemia

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.

Contents

1 Guidance

1.1 Idelalisib, in combination with rituximab, is recommended:

- for untreated chronic lymphocytic leukaemia in adults with a 17p deletion or TP53 mutation or
- for chronic lymphocytic leukaemia in adults when the disease has been treated but has relapsed within 24 months.

  Idelalisib is recommended only if the company provides the drug with the discount agreed in the simple discount agreement.

1.2 People whose treatment with idelalisib is not recommended in this NICE guidance but was started within the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Idelalisib (Zydelig, Gilead Sciences) is a first-in-class inhibitor of enzymes that regulate important cellular functions including proliferation, cell death and migration. It has a marketing authorisation in the UK for use 'in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia who have received at least 1 prior therapy, or as first-line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy'.

2.2 The summary of product characteristics lists the following adverse reactions to idelalisib, alone or with rituximab, as affecting more than 10% of patients: infections, neutropenia, diarrhoea, transaminase increase, rash, pyrexia and increased triglycerides. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The recommended dose and schedule in the summary of product characteristics is 150 mg taken orally, twice daily. Treatment is continued until disease progression or unacceptable toxicity; in most cases, treatment can be resumed at 100 mg twice daily when the adverse event has been resolved. Idelalisib is priced at £3114.75 for 60 150-mg tablets (British National Formulary 2015). The mean cost of a 1-year treatment course for idelalisib is £37,922. The company has a simple discount agreement that provides a discount to the list price of idelalisib. The level of the discount is commercial in confidence.

3 The company's submission

The Appraisal Committee (section 7) considered evidence submitted by Gilead Sciences and a review of this submission by the Evidence Review Group (ERG; section 8).

Clinical effectiveness evidence

Systematic review

3.1 The company's systematic literature review identified 6 randomised controlled trials that were relevant to the decision problem because they included patients whose disease was relapsed or refractory. The company noted that none of the trials identified in the literature review compared idelalisib plus rituximab directly with the appropriate comparators identified in the NICE scope.

3.2 One single arm study was identified that investigated the effectiveness of idelalisib with rituximab in untreated chronic lymphocytic leukaemia in patients with a 17p deletion or TP53 mutation.

Previously treated chronic lymphocytic leukaemia (Study 116)

3.3 The company presented the results of Study 116, which was a phase III, double-blind, randomised controlled trial across 90 centres in the US and Europe (including the UK). The study evaluated idelalisib plus rituximab compared with rituximab plus placebo in people with chronic lymphocytic leukaemia. A total of 220 patients were randomised to either idelalisib (150 mg oral tablets, twice daily) plus rituximab (375 mg/m^2 at week 0, then 500 mg/m^2 at weeks 2, 4, 6, 8, 12, 16 and 20) or rituximab (same dose) plus placebo (matching tablet, twice daily, until progression or withdrawal due to tolerability issues). Patients were included if they were aged 18 years or older, had previously had at least 1 treatment line (either an anti-CD20 or 2 or more cytotoxic regimens) and had a reported Karnofsky performance score of 40 or more. Patients were excluded if their disease had a known histological transformation from chronic lymphocytic leukaemia to a more aggressive lymphoma.

3.4 The primary outcome of Study 116 was progression-free survival, defined as the interval from randomisation to first documentation of definitive disease progression or death from any cause (whichever was sooner). Definitive disease

progression was defined using the criteria from the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL). Secondary outcomes included rates of overall response (complete and partial), lymph node response (defined as a decrease of 50% or more in lymphadenopathy) and overall survival. The primary and secondary end points were examined in pre-specified subgroups, including: the presence or absence of a 17p deletion, TP53 mutation or both; sex (male or female); and age (less than 65 years or more than 65 years old). Health-related quality of life was assessed using a change in domain and symptom scores from the Functional Assessment of Cancer Therapy: Leukaemia (FACT-Leu) instrument, and using the EQ-5D instrument. These were administered at baseline and at each study visit.

3.5 Patients could cross over from the rituximab plus placebo group to having idelalisib monotherapy in an extension study if their disease progression were confirmed by an independent review committee. The intention-to-treat analysis was done according to the treatment to which patients were randomised, and this included patients who had crossed over to the idelalisib monotherapy group. Progression-free survival was calculated using the Kaplan–Meier method. A Cox proportional hazards model with adjustment for stratification was used to calculate hazard ratios.

Results of Study 116

3.6 The company stopped the blinded phase of the trial after the first interim analysis, because the 2-sided p-value for the primary progression-free survival analysis crossed the prespecified alpha boundary of 0.001. All 110 patients in the idelalisib plus rituximab group and 107 of 110 in the rituximab plus placebo group had the assigned treatment. Of the 3 patients in the rituximab plus placebo group who did not have the study treatment, 2 withdrew from the study because of an adverse event before study treatment was started and 1 had not had the study treatment before the data cut-off. The mean age of patients in the trial was 71 years. Between 41.8% and 44.5% of patients had a 17p deletion or TP53 mutation (or both), and 82.7% to 84.5% had an immunoglobulin variable region heavy chain non-mutation.

3.7 The results showed a statistically significant improvement in median progression-free survival for idelalisib plus rituximab compared with rituximab plus placebo of 19.4 months (95% confidence interval [CI] 12.3, not reported)

compared with 6.5 months (95% CI 4.0 to 7.3). The reported hazard ratio (HR) was 0.15 (95% CI 0.09 to 0.24, p=<0.001). The intention-to-treat analysis for median overall survival showed a statistically significant difference for idelalisib plus rituximab compared with rituximab plus placebo (HR 0.34, 95% CI 0.19 to 0.60, p=<0.001).

3.8 In terms of secondary outcomes, the overall response rate was 83.6% for idelalisib plus rituximab compared with 15.5% for rituximab plus placebo. The odds ratio for overall response for idelalisib with rituximab compared with rituximab was 27.76 (95% CI 13.4 to 57.49). No patients in the trial had a complete response, meaning that the overall response rate was entirely made up of partial responders. The lymph node response rate was 96.2% in the idelalisib plus rituximab group compared with 6.7% in the rituximab plus placebo group.

3.9 The company also presented the results for the prespecified subgroups. In patients without a 17p deletion or TP53 mutation, median progression-free survival was 19.4 months in the idelalisib plus rituximab group compared with 8.1 months in the rituximab plus placebo group. For people with a 17p deletion or TP53 mutation, progression-free survival was not reached in the idelalisib plus rituximab group. In the rituximab plus placebo group, median progression-free survival was 4.0 months.

3.10 Patients having idelalisib plus rituximab showed improvements in health-related quality of life, with the EQ-5D analysis showing a statistically significant treatment effect. The results of the FACT-Leu questionnaire also showed that patients in the idelalisib plus rituximab group had greater symptom improvement than patients in the rituximab group at each time point throughout the trial.

3.11 The company reported that 15 patients had treatment-emergent adverse events that led to death (4 having idelalisib plus rituximab, 11 having rituximab plus placebo). It noted that the causes of death were consistent with advanced chronic lymphocytic leukaemia and the underlying frailty, age, and poor prognosis of the study population.

3.12 The company reported that 32 patients – 19 (17.3%) of those having idelalisib plus rituximab and 13 (12.0%) of those having rituximab plus placebo –

discontinued treatment because of an adverse event. Infections and infestations occurred in 11 of the 32 patients who discontinued (5 having idelalisib plus rituximab and 6 having rituximab plus placebo) and gastrointestinal disorders occurred in 6. Respiratory, thoracic, and mediastinal disorders accounted for a further 6 patients discontinuing because of adverse events (3 having idelalisib plus rituximab and 3 having rituximab plus placebo).

3.13 The company noted that the most commonly reported adverse events in the idelalisib plus rituximab group were: pyrexia (40.0%, 44 patients), fatigue (30.9%, 34 patients), diarrhoea (29.1%, 32 patients), nausea (27.3%, 30 patients) and neutropenia (25.5%, 28 patients). The most commonly reported adverse events in the rituximab plus placebo group were fatigue (33.3%, 36 patients), cough (31.5%, 34 patients) and infusion-related reactions (30.6%, 33 patients).

Untreated chronic lymphocytic leukaemia with a 17p deletion or TP53 mutation (Study 101-08)

3.14 Study 101-08 was a phase II, single-arm study of idelalisib plus rituximab in patients with untreated chronic lymphocytic leukaemia. A total of 64 patients were enrolled in centres across the US to have idelalisib (150 mg oral tablets, twice daily) and rituximab (375 mg/m^2 for 8 weeks of continuous treatment). Only a small subset of patients (n=9) had a 17p deletion or TP53 mutation.

3.15 The primary outcome of the study was overall response rate, which was defined as the proportion of patients who achieved a complete or partial response as defined according to IWCLL criteria. Secondary outcomes included adverse events, progression-free survival and overall survival.

Results of Study 101-08

3.16 Of the 64 patients who were enrolled, 43 completed 48 weeks of treatment. The mean age of patients in the trial was 71 years. Only 9 of the 64 patients had a 17p deletion or TP53 mutation, and 37 had immunoglobulin heavy-chain variable-region non-mutated chronic lymphocytic leukaemia.

3.17 At 36 months no patients with a 17p deletion or TP53 mutation had a progression event. Progression-free survival for the overall population at 36 months was 83%, compared with 100% for the 17p deletion or TP53 mutation patients. Overall survival at 36 months was 100% for the

17p deletion or TP53 mutation patients and 90% for the whole study population.

3.18 The company noted that all 64 patients in the trial had 1 dose or more of the study drug. The most common treatment-emergent adverse events were diarrhoea or colitis (77%), rash (58%) and pyrexia (42%).

Evidence for other comparators listed in the NICE scope

3.19 In addition to the comparison of idelalisib plus rituximab with rituximab alone, best supportive care and ofatumumab, the company also submitted evidence for the other comparator technologies listed in the NICE scope, namely fludarabine cyclophosphamide plus rituximab, bendamustine with or without rituximab, chlorambucil with or without rituximab, and steroids plus rituximab. The company's systematic review did not identify any evidence directly comparing idelalisib with these comparators, but identified 5 randomised controlled trials and 13 non-randomised controlled trials in the relapsed or refractory population. One randomised controlled trial was identified in the untreated population.

ERG comments

3.20 The ERG commented on the population of Study 116 and its applicability to people with chronic lymphocytic leukaemia in the UK (of the 220 patients enrolled, 32 were UK patients). It noted that the trial included some patients (43.2%) with a 17p deletion or TP53 mutation; this type of disease does not respond to standard chemotherapy. The ERG noted that the baseline characteristics of patients in the trial represented a high-risk patient cohort. The ERG also noted that the use of rituximab as a comparator was limited in its relevance to a UK population, because it is neither recommended by NICE nor by the British Committee on Standards in Haematology guidance.

3.21 The ERG noted that the results of Study 116 should be interpreted with caution because the trial was stopped early for benefit, and this type of stopping can lead to an overestimation of treatment effect.

Cost-effectiveness evidence

Economic model structure

3.22 The company submitted a de novo economic model for the relapsed or refractory chronic lymphocytic leukaemia population only. The company did not submit an economic model for the untreated group because of the limited evidence available from Study 101-08. The base-case analysis modelled the following:

- idelalisib plus rituximab compared with rituximab alone
- idelalisib plus rituximab compared with best supportive care
- idelalisib plus rituximab compared with ofatumumab.

3.23 The company included an additional exploratory analysis of idelalisib plus rituximab compared with the other comparators listed in the NICE scope:

- fludarabine, cyclophosphamide and rituximab
- bendamustine
- bendamustine plus rituximab
- chlorambucil
- chlorambucil plus rituximab
- steroids plus rituximab.

3.24 The company used a Markov model with time-dependent transition probabilities. It used weekly cycle lengths (with half-cycle corrections) with a time horizon of 25 years. The mean age of patients entering the model was 71 years. A discount rate of 3.5% was applied to costs and health benefits and the analysis was done from an NHS and personal social services perspective.

3.25 The base-case analysis used data from Study 116. The model consisted of 5 health states, namely pre-progression on treatment, pre-progression off treatment, post progression, terminal care and death. The on treatment state was determined by the area under parametric time-on-treatment curves. The

pre-progression off treatment and post-progression states were informed by the parametric survival curve analysis of progression-free and overall survival data.

Clinical parameters and assumptions

3.26 To inform the clinical parameters for idelalisib plus rituximab compared with ofatumumab, the company assumed equal efficacy for rituximab and ofatumumab. The company explained that this assumption reflected the results of the ORCHARRD study, a network meta-analysis in patients with diffuse large B-cell lymphoma which found no difference in efficacy between ofatumumab and rituximab. The company also assumed equal efficacy for rituximab and best supportive care because there were insufficient data available to model this comparator.

3.27 To inform the model transition probabilities, the company extrapolated the overall survival data beyond the trial cut-off. The company used the crossover-adjusted overall survival data from Study 116 (patients could crossover from the rituximab plus placebo group to instead have idelalisib plus rituximab). The company used the Akaike Information Criterion statistic (an indication of the statistical fit between the observed Kaplan–Meier data and the parametric model estimates) to assess the most appropriate functional form. The results of the analyses showed that the exponential model provided the most appropriate fit, followed by the Weibull. The company explained that, on inspection of the model, 5% of patients were still alive after 20 years which it deemed inappropriate. The company therefore chose the Weibull model, as the next best fit, to extrapolate the overall survival data.

3.28 The company explained that progression-free survival data did not need to be adjusted for crossover before extrapolation, because disease progression in the trial was the main reason for patients crossing over to the idelalisib plus rituximab group. The Akaike Information Criterion statistic suggested that the Weibull model was the most appropriate curve to use to extrapolate beyond the trial data.

3.29 The company used time-on-treatment data from Study 116 to estimate the drug resource use for idelalisib in the pre-progression on treatment state. In the trial, idelalisib was indicated to be taken until disease progression or

unacceptable toxicity, so the company noted that time on treatment followed a similar course to progression-free survival. To extrapolate the data, it determined that a Cox proportional hazards model should be used to calculate a hazard ratio for time on treatment compared with progression-free survival. This produced a hazard ratio of 1.31. It then applied this to the progression-free survival curve for idelalisib plus rituximab to derive a time-on-treatment curve. For consistency, the company used the same hazard ratio to estimate a time-on-treatment curve for the rituximab plus placebo group of Study 116.

3.30 The company used the overall response rates reported in Study 116 to inform resource use assumptions in the model. The overall response rates were 84% in the idelalisib plus rituximab group and 15% in the rituximab plus placebo group. For the comparison with best supportive care, patients were assumed to have no overall response. For the comparison with ofatumumab, the overall response rate for rituximab plus placebo was applied.

Other comparators listed in the NICE scope

3.31 The company identified additional evidence from the literature for the other comparators listed in the NICE scope (table 1). It selected those studies which reported overall survival and progression-free survival so it could extrapolate the data over the model time horizon. No studies were identified for the comparison with chlorambucil or chlorambucil plus rituximab, so the company used data from a published phase III trial (Knauf et al.) in patients with untreated chronic lymphocytic leukaemia and applied the reported hazard ratios to the bendamustine and bendamustine plus rituximab survival curves. The company assumed a shape parameter equal to that estimated for treatment arm data from Study 116, in which patients had idelalisib plus rituximab, to allow estimation of survival curves for the exploratory comparisons to external trial data. Treatment arm data were chosen because, unlike comparator arm data, these had not been confounded by crossover. The company validated the curves by visual inspection against the Kaplan–Meier data reported in the studies. It also adjusted for differences in baseline characteristics between the different studies.

Table 1 Results of the studies used to inform the company's additional comparator analysis

Treatment regimen	Median overall survival (months)	Median progression-free survival (months)	Number of patients	Study design
Fludarabine, cyclophosphamide and rituximab	47	21	284	Open-label, phase II study (Badoux 2011)
Bendamustine	44	20	49	Open-label randomised controlled trial (Niederle 2013)
Bendamustine plus rituximab	34	15	78	Open-label, phase II study (Niederle 2013)
Steroids plus rituximab	31	12	29	Single-arm open-label study (Pileckelyte 2011)
Ofatumumab	15	6	79	Single-arm open-label study (Wierda 2010)

Utility values and adverse events

3.32 The company used EQ-5D data collected alongside Study 116 to inform the utility values for patients in the pre-progression on treatment state. It used a generalised estimation equation regression to determine whether there was a difference in quality of life between the study groups. The company also assumed that utility values in the terminal care state were equal to those in the post-progression state. However, no EQ-5D trial data were collected for patients in the post-progression or post-treatment discontinuation states, so the company conducted a systematic literature review to identify studies reporting utility values for different chronic lymphocytic leukaemia health states. The company identified a range of studies, and chose to use Dretzke et al. (2010) for the post-progression and pre-progression off treatment states.

3.33 The company derived adverse event frequencies directly from Study 116. Those considered in the model were grade 3 or 4 events which occurred in at least 3% of patients in either treatment groups of Study 116.

Resource use and costs

3.34 The company used the time-on-treatment curves from Study 116 to estimate the length of time patients would have idelalisib plus rituximab and rituximab alone in the pre-progression on treatment state. The company used the same dosing regimen from Study 116 for idelalisib plus rituximab and rituximab alone. For the other comparators, treatment costs were applied to the proportion of patients remaining in the progression-free health states in the model, up to maximum treatment durations. The proportion of modelled patients who progressed before maximum treatment durations were not assumed to complete the full course of treatment.

3.35 Based on expert advice, the company assumed that intravenous immunoglobulin therapy would be used in 45% of non-responders and 0% of responders in the pre-progression health states. The company estimated that the cost of intravenous immunoglobulin therapy, incorporating the acquisition cost and administration of 5 weekly infusions, was £13,706. Active treatment was assumed to be every 3.5 weeks, based on British Committee for Standards in Haematology guidelines.

Company's base-case results and sensitivity analyses

3.36 When using the simple discount agreement price for idelalisib, treatment with idelalisib plus rituximab was associated with higher costs and greater quality-adjusted life year (QALY) gains compared with rituximab alone. The deterministic incremental cost-effectiveness ratio (ICER) for idelalisib plus rituximab compared with rituximab alone was £13,634 per QALY gained (incremental costs £26,128; incremental QALYs 1.92). Compared with best supportive care, the ICER for idelalisib plus rituximab was £20,461 per QALY gained (incremental costs £39,211; incremental QALYs 1.92). Compared with ofatumumab, the ICER was £1527 per QALY gained (incremental costs £2926; incremental QALYs 1.92).

3.37 The company conducted a range of deterministic sensitivity analyses on the base-case parameters. The results showed that the survival curve parameter estimates had the greatest influence on the results.

3.38 The company conducted a probabilistic sensitivity analysis for the base-case parameters, presenting scatter plots and cost-effectiveness acceptability curves for the 3 base-case comparisons. The results showed that idelalisib plus rituximab was cost effective with a 90% probability compared with rituximab alone, an 80% probability compared with best supportive care, and a 100% probability compared with ofatumumab (at a maximum acceptable ICER of £30,000 per QALY gained). The mean probabilistic ICER for the comparison of idelalisib plus rituximab with rituximab alone was £13,680 per QALY gained. For idelalisib plus rituximab compared with ofatumumab, the mean probabilistic ICER was £1692 per QALY gained; for the comparison with best supportive care, it was £20,021 per QALY gained. The mean probabilistic ICER for the comparison of idelalisib plus rituximab with rituximab alone was £13,680 per QALY gained. For the comparison with ofatumumab, the mean probabilistic ICER was £1692 per QALY gained; for the comparison with best supportive care, it was £20,021 per QALY gained.

Company's exploratory scenarios

3.39 When using the simple discount agreement price for idelalisib, treatment with idelalisib plus rituximab was associated with both higher costs and greater QALY gains compared with:

- fludarabine, cyclophosphamide and rituximab: £26,215 per QALY gained (incremental costs £63,232; incremental QALYs 2.41)
- bendamustine: £36,424 per QALY gained (incremental costs £49,677; incremental QALYs 1.36)
- bendamustine plus rituximab: £21,910 per QALY gained (incremental costs £35,910; incremental QALYs 1.64)
- chlorambucil: £33,224 per QALY gained (incremental costs £55,471; incremental QALYs 1.67)
- chlorambucil plus rituximab: £35,082 per QALY gained (incremental costs £66,267; incremental QALYs 1.89)

- steroids plus rituximab: £17,106 per QALY gained (incremental costs £23,689; incremental QALYs 1.38)
- ofatumumab (clinical effectiveness from literature): £4,254 per QALY gained (incremental costs £8232; incremental QALYs 1.96).

3.40 The company presented a subgroup analysis for patients in Study 116 with a 17p deletion or TP53 mutation. The results showed an increase in the ICERs for all 3 base-case comparators: £20,200 per QALY gained for the comparison with rituximab alone, £27,543 per QALY gained for the comparison with best supportive care and £7066 per QALY gained for the comparison with ofatumumab.

ERG comments

3.41 The ERG noted the company's assumption that treatment effects continue beyond the trial. The ERG acknowledged that the treatment benefits of idelalisib may continue beyond the time horizon of the trial, but would be unlikely to continue for the rest of a patient's life. It noted that any reduction in treatment benefit following a discontinuation could result in a smaller treatment benefit for idelalisib with rituximab compared with the other regimens.

3.42 The ERG highlighted a possible issue with the company's methodology to adjust for crossover in the trial, noting that the company's analysis relies on the assumption that idelalisib alone has equal efficacy to idelalisib plus rituximab. It stated that a lower efficacy for idelalisib alone would result in a lower treatment benefit for idelalisib plus rituximab compared with rituximab and the magnitude of this change would only be substantial if idelalisib alone is considered inferior to idelalisib plus rituximab.

3.43 The ERG commented on the company's use of the constant shape parameter for the survival curves for the other treatments. It noted that the company could have fitted survival models directly using the digitised Kaplan–Meier plots that were generated. The ERG noted that this would improve the extrapolation for the fludarabine, cyclophosphamide and rituximab data, where the model (assuming a constant shape) was a poor fit for the data. In addition, the ERG questioned why the company had chosen to use hazard ratios from Badoux et

al. to adjust for baseline differences in its extrapolations instead of the other studies identified in the literature review.

3.44 The ERG noted that in the company's base case, costs for idelalisib, rituximab and ofatumumab were accrued until treatment discontinuation, but for other comparators patients were assumed to complete the full maximum dosing indicated for that product. The ERG stated that a more realistic approach would be to use time-on-treatment data from Study 116 to estimate the proportion of the maximum number of doses actually administered for rituximab monotherapy, in the same way as was done for idelalisib, and apply the costs to these estimated time-on-treatment data.

3.45 The ERG noted that because no attempt was made to account for differences between the study populations and UK patients, the results of the company's analyses may be uncertain. In addition, it noted that the plausibility of the results may be affected by assuming that ofatumumab and best supportive care have equal efficacy to rituximab alone. Finally, the ERG stated that even though the methodology used to conduct the analyses for the other comparators in the NICE scope was less reliable than that used in the formal evidence synthesis, many of the comparators are used in the UK and therefore results from these analyses (with appropriately conservative assumptions) are important to understanding the cost-effectiveness of idelalisib compared with other available treatments.

3.46 The ERG raised concerns with the assumptions relating to the frequency of resource use parameters, specifically about the number of patients whose disease did not respond to treatment being given intravenous immunoglobulin therapy. The ERG noted that this is important because the biggest difference in clinical outcomes between idelalisib plus rituximab and rituximab alone was the overall response rate. This meant that the clinical assumptions made in the model resulted in considerably higher disease management costs for patients having rituximab alone than those having idelalisib plus rituximab.

3.47 The ERG highlighted that utility values for patients who had discontinued treatment with idelalisib plus rituximab (taken from Dretzke et al.) in the pre-progression states remained higher than those for patients having rituximab alone. It noted that this difference was more than could be explained by the adverse event disutilities calculated from Study 116, and meant

that patients discontinuing idelalisib maintained a higher quality of life than those still having rituximab (an assumption not justified in the company submission)

ERG exploratory analyses

3.48 The ERG conducted an exploratory analysis changing the following parameters:

- Using the Dretzke et al. utility values to inform both the pre-progression and post-progression model states, instead of those collected alongside Study 116 for the pre-progression state.
- Using time-on-treatment data for rituximab monotherapy to inform estimated drug costs rather than assuming that all patients completed the full course. For treatments outside Study 116, patients were assumed to take the same proportion of the maximum dosing duration as for rituximab alone in Study 116.
- Using the statistically best fitting survival curve for fludarabine, cyclophosphamide and rituximab, rather than using the constant shape parameter with the curve for rituximab alone, as used in the company model.
- Changing the length of treatment benefit for agents other than rituximab to 5 years.

3.49 Applying the simple discount agreement price for idelalisib, treatment with idelalisib plus rituximab was associated with higher costs and greater QALY gains compared with:

- rituximab: £16,947 per QALY gained (incremental costs £24,335; incremental QALYs 1.44)
- best supportive care: £26,058 per QALY gained (incremental costs £37,418; incremental QALYs 1.44)
- ofatumumab (base case): £788 per QALY gained (incremental costs £1132; incremental QALYs 1.44)
- fludarabine, cyclophosphamide and rituximab: £33,795 per QALY gained (incremental costs £71,177; incremental QALYs 2.11)
- bendamustine: £52,815 per QALY gained (incremental costs £48,821; incremental QALYs 0.92)

- bendamustine plus rituximab: £29,548 per QALY gained (incremental costs £34,921; incremental QALYs 1.18)
- chlorambucil: £44,315 per QALY gained (incremental costs £53,779; incremental QALYs 1.21)
- chlorambucil plus rituximab: £45,445 per QALY gained (incremental costs £64,893; incremental QALYs 1.43)
- steroids plus rituximab: £24,065 per QALY gained (incremental costs £22,751; incremental QALYs 0.95)
- ofatumumab (clinical effectiveness from literature): £5355 per QALY gained (incremental costs £8006; incremental QALYs 1.49).

3.50 The ERG did an additional analysis exploring the frequency of intravenous immunoglobulin therapy for patients whose disease responds to treatment compared with patients whose disease does not respond. In the company's model, 45% of patients whose disease does not respond had 1.24 cycles of intravenous immunoglobulin therapy. Patients whose disease does respond had none at all. The ERG explored increasing the number of cycles to responders and decreasing the number of cycles for non-responders. The results showed that the ICER was sensitive to the changes; when responders had 0.5 cycles of intravenous immunoglobulin and non-responders had 1.0 cycle, the ICER for idelalisib with rituximab compared with rituximab alone increased from £16,947 per QALY gained to £52,369 per QALY gained.

New evidence submitted by the company following consultation

3.51 Following a request by the Appraisal Committee in the appraisal consultation document (ACD), the company submitted a revised cost-effectiveness analysis. The revised analysis compared idelalisib plus rituximab with rituximab alone, best supportive care and ofatumumab and incorporated the following changes to the base-case analysis:

- The overall survival benefit for idelalisib plus rituximab, predicted by extrapolating overall survival data from Study 116, was restricted to 5 years.
- Using utility values from Dretzke et al. (2010) instead of Study 116 EQ-5D data for all pre-progression health states.

In addition, the company provided sensitivity analyses:

- exploring the effect of reducing treatment benefit with idelalisib from 5 years to 3 years
- exploring the proportion of patients assumed to have intravenous immunoglobulin therapy
- using clinical data from the subgroup of patients from Study 116 whose disease was refractory.

3.52 The company submitted 2 more economic analyses. The first, called the 'corrected base-case analysis', included the changes requested in section 3.51 but made a correction to the dosing of intravenous immunoglobulin therapy. The company explained that in its original base case, the cost of intravenous immunoglobulin therapy was estimated assuming a dose of 0.4 g/kg administered 5 times for 1 active treatment week, and included administration costs for 5 infusions. However, the company noted that this assumption was based on the estimated dosing for diseases other than chronic lyphocytic leukaemia and the appropriate dosing for this condition, according to the Department of Health's clincal guidelines for immunoglobulin use, is 0.4 g/kg of therapy administered once.

3.53 The second additional analysis submitted by the company, called the 'proposed base case', also incorporated the requested analyses in section 3.51 and the changes in the dosage of intravenous immunoglobulin therapy as described in section 3.52, but reverted back to using Study 116 EQ-5D data for patients in the pre-progression model state.The company noted the ERG's comments on its original base-case analysis (see section 3.47) which stated that patients in the pre-progression model state who discontinued idelalisib treatment were assumed to maintain a permanently higher health related quality of life than those who had rituximab (until disease progression). The company addressed this issue in the proposed base case by assigning the utility from the rituximab arm of Study 116 to those patients discontinuing from idelalisib treatment.

3.54 The results of the proposed base-case analysis, when using the simple discount agreement price for idelalisib, showed that treatment with idelalisib plus rituximab was associated with higher costs and greater QALY gains compared with rituximab alone. The deterministic ICER for idelalisib plus rituximab

compared with rituximab alone was £26,403 per QALY gained (incremental costs £38,933; incremental QALYs 1.47). Compared with best supportive care, the ICER for idelalisib plus rituximab was £35,275 per QALY gained (incremental costs £52,016; incremental QALYs 1.47). Compared with ofatumumab, the ICER was £10,668 per QALY gained (incremental costs £15,731; incremental QALYs 1.47).

3.55 The results of the sensitivity analysis exploring the effect of reducing the proportion of non-responders having intravenous immunoglobulin therapy to 20% and increasing the proportion of responders having the therapy to 20% showed the following:

- For the comparison of idelalisib plus rituximab with rituximab alone, the ICERs ranged from £27,773 per QALY gained to £34,869 per QALY gained.
- For the comparison of idelalisib with best supportive care, the ICERs ranged from £36,645 per QALY gained to £43,742 per QALY gained.
- For the comparison of idelalisib with ofatumumab, the ICERS ranged from £12,038 per QALY gained to £19,134 per QALY gained.

3.56 The results of the sensitivity analysis exploring the effect on reducing the treatment benefit with idelalisib from 5 years to 3 years showed the following:

- For the comparison of idelalisib plus rituximab with rituximab alone, the ICER ranged from £26,403 per QALY gained with a 5-year limit to £33,850 per QALY gained with a 3-year limit.
- For the comparison of idelalisib with best supportive care, the ICERs ranged from £35,275 per QALY gained with a 5-year limit to £45,674 per QALY gained with a 3-year limit.
- For the comparison of idelalisib with ofatumumab, the ICERs ranged from £10,668 per QALY gained for a 5-year limit to £12,880 per QALY gained with a 3-year limit.

ERG comments

3.57 The ERG reviewed the new evidence submitted by the company. It validated the company's revised base-case analysis (see 3 .51) against the results it produced (sections 3.48–3.49). Although the results were not identical (£16,977 per

QALY gained compared with £16,947 per QALY gained for idelalisib plus rituximab compared with rituximab alone), they were similar and the ERG had no concerns about the validity of the new results submitted.

3.58 The ERG reviewed the results of the proposed base case. It noted the changes to both the assumptions for intravenous immunoglobulin dosing (see section 3.52) and the changes to the utility values (see section 3.53), and considered them appropriate. However, the ERG highlighted that apart from the sensitivity analysis exploring the proportion of patients having intravenous immunoglobulin therapy, the company had continued to assume that 45% of non-responders and 0% of responders have the therapy in all the analyses.

3.59 The ERG reviewed the results of the probabilistic sensitivity analysis for the comparisons in the proposed base-case analysis. The results indicated that the proposed base case was highly sensitive to the cost at which treatments were considered to be cost effective. Although idelalisib plus rituximab was cost effective compared with rituximab alone in 97% of simulations at £50,000 per QALY, it was only cost effective in 62% and 12% of simulations at £30,000 and £20,000 per QALY respectively. The equivalent results for idelalisib plus rituximab compared with best supportive care were 88% at £50,000 per QALY, 22% at £30,000 per QALY and 0% at £20,000 per QALY.

3.60 The ERG conducted further analyses on the results of the company's proposed base case to generate ICERs for idelalisib plus rituximab compared with the other comparators listed in the NICE scope. The results of these analyses showed that the ICERs for idelalisib plus rituximab (using the simple discount agreement price for idelalisib) were:

- £25,106 per QALY gained compared with fludarabine, cyclophosphamide and rituximab
- £28,284 per QALY gained compared with steroids plus rituximab
- £32,607 per QALY gained compared with bendamustine plus rituximab
- £34,922 per QALY gained compared with chlorambucil plus rituximab
- £44,302 per QALY gained compared with chlorambucil alone
- £49,523 per QALY gained compared with bendamustine alone.

3.61 The ERG did an exploratory analysis to examine the effect on the ICERs (for the comparisons outside of Study 116) when changing the proportions of patients who had intravenous immunoglobulin therapy. The results of these analyses showed that the ICERs for idelalisib plus rituximab (using the simple discount agreement price for idelalisib) when 20% of non-responders and 10% of responders had intravenous immunoglobulin therapy were:

- £26,484 per QALY gained compared with fludarabine, cyclophosphamide and rituximab
- £32,566 per QALY gained compared with steroids plus rituximab
- £36,200 per QALY gained compared with bendamustine plus rituximab
- £36,398 per QALY gained compared with chlorambucil plus rituximab
- £48,074 per QALY gained compared with chlorambucil alone
- £51,937 per QALY gained compared with bendamustine alone.

3.62 Full details of all the evidence are available.

4 Consideration of the evidence

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

Clinical effectiveness

4.1 The Committee discussed the current clinical management of chronic lymphocytic leukaemia. The Committee heard from the clinical experts that treatment options for disease which has been previously treated depends on the person's suitability for certain treatments, the treatments they have already had and the time since the last disease relapse. The clinical experts advised that re-treatment with fludarabine-based regimens (such as fludarabine, cyclophosphamide and rituximab) or alkylating agents (such as bendamustine plus rituximab or chlorambucil plus rituximab) is suitable for people whose disease has relapsed more than 24 months after their last treatment. The clinical experts noted that for people whose disease had relapsed less than 24 months after their last treatment, options are limited. Re-treatment is less effective and can cause the disease to develop deletions and mutations which in turn lead to chemotherapy-resistant chronic lymphocytic leukaemia. The Committee also discussed the clinical management of untreated chronic lymphocytic leukaemia in people with a 17p deletion or TP53 mutation. It heard from the clinical experts that people with this type of disease have very limited treatment options, which can include high-dose pulsed steroids with alemtuzumab. The Committee concluded that more treatment options are needed.

4.2 The Committee considered the population in the marketing authorisation which included people with chronic lymphocytic leukaemia whose disease has been previously treated and people with a 17p deletion or TP53 mutation whose disease is untreated. The Committee discussed whether there were different subgroups in the population of people with previously treated chronic lymphocytic leukaemia that should be considered separately. It noted that the British Committee for Standards in Haematology defines relapse as disease progression at least 6 months after achieving a complete response or partial response. The Committee noted comments received during consultation that

relapsed disease can be further subdivided into those whose disease relapses more than 24 months after their last treatment and those whose disease relapses less than 24 months after their last treatment. The Committee further noted that the British Committee for Standards in Haematology defines refractory disease as treatment failure or disease progression within 6 months of treatment. The Committee concluded that for the purposes of this appraisal, the following populations should be considered:

- People whose disease has been previously treated and has relapsed more than 24 months after treatment.
- People with high-risk relapsed disease whose disease has been previously treated and has relapsed less than 24 months after treatment.
- People with refractory disease whose disease has failed treatment or relapsed less than 6 months after treatment.
- Untreated disease with a 17p deletion of TP53 mutation.

4.3 The Committee considered the relevant comparators listed in the NICE scope for people whose disease has relapsed. The Committee heard from the clinical experts about the available treatment options and concluded that in people whose disease had relapsed more than 24 months since their last treatment, the relevant comparators were fludarabine, cyclophosphamide and rituximab (if suitable), bendamustine (with or without rituximab) or chlorambucil (with or without rituximab). The Committee then considered the relevant comparators for people whose disease is high risk and relapsed. The Committee heard from the clinical experts that re-treatment options are the same for people with relapsed chronic lymphocytic leukaemia but that multiple retreatments with chemotherapy agents in high-risk relapsed disease can become ineffective and lead to TP53 abnormalities, which in turn lead to treatment resistance. The Committee was aware that ofatumumab had been included as a comparator in the NICE scope. The Committee acknowledged comments received during consultation from a comparator company, which noted that ofatumumab is no longer available through the Cancer Drugs Fund and is not recommended for use in the previously treated setting. The Committee therefore concluded that the relevant comparators for people with high-risk relapsed chronic lymphocytic leukaemia were fludarabine, cyclophosphamide and rituximab (if suitable), bendamustine (with or without rituximab), or chlorambucil (with or without rituximab). In people whose disease is refractory, the Committee heard

from the clinical experts that rituximab alone or best supportive care was the only treatment option. The Committee was aware that rituximab alone had not been included as a comparator in the NICE scope but concluded that rituximab could be considered a relevant comparator in people whose disease is refractory because of the limited treatment options available to them. The Committee considered the relevant comparators for people with untreated disease and a 17p deletion or TP53 mutation. It heard from the clinical experts that chemotherapy is not suitable for these people because it causes further deletions and mutations to occur. Alemtuzumab with or without steroids is a treatment option, but its marketing authorisation was recently withdrawn and access to the drug for treating chronic lymphocytic leukaemia is limited. The Committee therefore concluded that for people with untreated disease and a 17p deletion or TP53 mutation, active treatment options are very limited.

4.4 The Committee heard from the clinical and patient experts about the adverse effects of the available treatments for chronic lymphocytic leukaemia. The patient experts described how the toxicity of fludarabine-containing regimens often makes them inappropriate for older people who may have comorbidities. It heard that treatments such as chlorambucil, steroids or ofatumumab are easier to tolerate, but in some patients produce only short periods of remission. The clinical experts also noted that alemtuzumab can cause serious adverse effects, including an ongoing risk of infection. The Committee heard from the clinical experts that idelalisib is associated with fewer adverse effects compared with other treatments for chronic lymphocytic leukaemia. The patient experts emphasised that patients prefer oral treatments like idelalisib. The Committee also heard that because patients are on life-long treatment, the uncertainty of living with chronic lymphocytic leukaemia brings psychological and emotional issues as well as physical ill-health. The Committee concluded that the available treatment options for chronic lymphocytic leukaemia are associated with undesirable adverse effects and further treatment options that do not result in the same or similar adverse effects would be welcomed.

4.5 The Committee considered the evidence submitted by the company for idelalisib plus rituximab compared with rituximab alone. It noted that Study 116 included only those people with previously treated high-risk relapsed (relapse less than 24 months since previous treatment) or refractory chronic lymphocytic leukaemia. The Committee noted the results of Study 116, which showed that idelalisib plus rituximab had a statistically significant improvement

in progression-free survival and overall survival compared with rituximab (see section 3.7). The Committee considered the generalisability of the results to patients in the UK with chronic lymphocytic leukaemia. It noted that the baseline characteristics of patients in the trial represented a high-risk patient cohort who had taken an average of 3 prior therapies (see section 3.20). In addition, 43.2% of patients in the trial had a 17p deletion or TP53 mutation. The Committee concluded that idelalisib plus rituximab provided a notable statistically significant improvement in progression-free survival and overall survival compared with rituximab for people whose disease is high-risk relapsed or refractory. The Committee further concluded that because no evidence had been submitted for people whose disease had relapsed more than 24 months after previous treatment, the results of Study 116 could not be used to inform its decision-making for this subgroup of people.

4.6 The Committee considered the evidence submitted by the company on the clinical effectiveness of idelalisib plus rituximab in people whose disease was untreated and who had a 17p deletion or TP53 mutation (see sections 3.14–3.18). It noted that the evidence for this population was limited because it was based on a single-arm trial (Study 101-08) of 64 patients, only 9 of whom had a 17p deletion or TP53 mutation. The Committee noted the results of the trial, which showed that at 36 months none of the patients having idelalisib plus rituximab had disease progression. It heard from the company that idelalisib's marketing authorisation had been granted partly on evidence from Study 116 (because a large proportion of patients [43.2%] had a 17p deletion or TP53 mutation), in addition to the evidence from Study 101-08. The Committee considered comments received during the appraisal consultation. It heard that because the number of patients living with this type of chronic lymphocytic leukaemia is small, conducting an adequately powered trial is not possible. The Committee was also aware that this group of patients had no treatment options available to them (see section 4.1). The Committee therefore concluded that the results of Study 101-08 could be used to at least partly inform its decision-making for this subgroup of patients.

4.7 The Committee considered the company's rationale for not submitting an indirect or mixed treatment comparison of idelalisib plus rituximab compared with the other comparators listed in the NICE scope. It heard from the ERG, which agreed with the company that a network could not be formed within the current evidence base. The Committee heard from the company that in the

absence of an indirect comparison, in order to proceed with the economic modelling for the other comparators listed in the NICE scope (fludarabine cyclophosphamide and rituximab, bendamustine with or without rituximab, chlorambucil with or without rituximab, steroids plus rituximab) it had provided an additional analysis following a systematic literature review (see section 3.31). The Committee was aware that the face validity of this approach had not been demonstrated and noted that the overall survival data for bendamustine plus rituximab were less than for bendamustine alone, which seemed counterintuitive. However, the ERG noted that in the absence of a network meta-analysis this was a suitable approach to take. The Committee accepted that a network meta-analysis was not possible for the indirect comparison of idelalisib plus rituximab compared with the other comparators in the NICE scope, and concluded that the company's alternative approach should be considered in the economic analysis.

Cost effectiveness

Economic model

4.8 The Committee considered the model presented by the company, the associated assumptions and the critique presented by the ERG. It noted that the company had submitted an economic model which addressed the population in Study 116 – that is, people with previously treated chronic lymphocytic leukaemia which is high-risk relapsed or refractory. The Committee recalled the clinical specialists' advice that treatments suitable for high-risk relapsed disease were: fludarabine, cyclophosphamide and rituximab; chlorambucil plus rituximab; or bendamustine plus rituximab. It was aware that there was no direct evidence for these comparators and an indirect comparison was not possible (see section 4.7). It further noted that the company had assumed that best supportive care had equal efficacy to rituximab alone, and heard from the clinical experts that this was a fair assumption. The Committee discussed the assumptions and concluded that the model was appropriate to inform its decision-making for people with high-risk relapsed and refractory disease. The Committee further noted that the company had not submitted any cost-effectiveness evidence for people with lower risk relapsed disease (that is, disease which has relapsed more than 24 months since treatment). The Committee therefore concluded that it could not make any recommendations for people who were outside the scope of Study 116.

4.9 The Committee considered the company's rationale for not submitting an economic model for people with untreated chronic lymphocytic leukaemia and a 17p deletion or TP53 mutation. It heard from the company that due to the limited evidence base it was not possible to conduct an economic evaluation using the results of Study 101-08 (see section 3.22). The Committee discussed the limitations of the available evidence base for the untreated population and concluded that an economic model could have been presented by the company. However, it noted that a proportion of patients in Study 116 (43.2%) had a TP53 mutation or 17p deletion (see section 4.5). It further noted the clinical experts' advice that in people with a 17p deletion or TP53 mutation, treatment with chemotherapy is ineffective and potentially harmful (see section 4.3). The Committee therefore concluded that it would consider its recommendations for the untreated group in the light of its decision of the cost-effectiveness results from the company's model for the high-risk relapsed groups.

4.10 The Committee considered the clinical effectiveness parameters used in the company's model. It heard from the ERG that the company's model contained an assumption that time on treatment was restricted, but that the benefits of treatment with idelalisib plus rituximab continued after both the time horizon of the trial and treatment discontinuation up to a maximum of 5 years. The Committee heard from the ERG that these assumptions may have overestimated the treatment effect of idelalisib plus rituximab. The Committee noted that the company had measured the effect of this assumption in its sensitivity analyses (see section 3.56). The Committee heard from the clinical experts that patients would continue to have treatment for chronic lymphocytic leukaemia until disease progression or until the treatment stopped working but that after stopping treatment, rebound deterioration could occur. The Committee concluded that the treatment benefit of idelalisib plus rituximab is unlikely to continue beyond treatment discontinuation, and therefore considered the most plausible assumption was to limit the treatment benefit of idelalisib plus rituximab, after treatment discontinuation, to 3 years.

4.11 The Committee considered the resource use assumptions in the company's model. It heard from the ERG that the company had assumed in the proposed base case that 45% of patients whose disease did not respond to treatment would have intravenous immunoglobulin therapy (see section 3.58). It heard from the clinical experts that this was an overestimate and that in clinical practice, up to 20% of patients whose disease did not respond to therapy would

have intravenous immunoglobulin therapy. The clinical experts also noted that intravenous immunoglobulin therapy is administered in up to 10% of patients whose disease did respond to treatment. The Committee concluded that in order to inform its decision-making, the most plausible estimate for the proportion of patients who would have intravenous immunoglobulin therapy is 20% for those whose disease does not respond treatment and 10% for those whose disease does respond to treatment.

4.12 The Committee considered the utility parameters used by the company in its economic model. It heard from the ERG that the company had used EQ-5D data collected alongside Study 116 for its pre-progression states and utilities from Dretzke et al. (2010) in its post-progression states (see section 3.32). The ERG highlighted that in the company's base case, patients who discontinued treatment maintained a permanently higher utility than in the rituximab alone group (see section 3.47). The ERG stated that it had explored using the Dretzke et al. (2010) values for both the pre-progression and post-progression states in its amendments to the company's base case, but that these changes did not have a notable effect on the incremental cost-effectiveness ratios (ICERs) for idelalisib plus rituximab compared with its comparators. Following the appraisal consultation the company submitted a proposed base case which used the EQ-5D trial data but corrected the errors identified by the ERG (see sections 3.51–3.56). The Committee heard from the ERG that these changes were appropriate (see section 3.58). The Committee therefore concluded that it was acceptable to use Study 116 EQ-5D data to inform the pre-progression utility values.

Most plausible ICER considerations

4.13 The Committee considered the most plausible ICER for idelalisib plus rituximab in people whose disease is high-risk relapsed. The Committee noted the results of the proposed base case and exploratory analysis for the comparisons of idelalisib plus rituximab (using the simple discount agreement price for idelalisib) with the relevant comparators for people with high-risk relapsed disease (see section 3.60). It noted that the ICERs ranged from £25,100 per quality-adjusted life year (QALY) gained (compared with fludarabine, cyclophosphamide and rituximab) to £34,900 per QALY gained (compared with chlorambucil plus rituximab). The Committee was aware that these analyses included the assumption that 45% of people whose disease does not

respond to treatment go on to have intravenous immunoglobulin therapy. It noted that when its preferred assumptions on intravenous immunoglobulin therapy usage were applied (see section 4.11), the ICER for the comparison with fludarabine, cyclophosphamide and rituximab increased to £26,500 per QALY gained, and for the comparison with chlorambucil plus rituximab the ICER increased to £36,400 per QALY gained (see section 3.61). The Committee was also aware that when its preferred assumption for treatment benefit of idelalisib plus rituximab following treatment discontinuation was applied (see section 4.10), the ICERs would likely increase further, up to a maximum of about £36,000 per QALY gained for the comparison with fludarabine, cyclophosphamide and rituximab and £46,000 per QALY gained for the comparison with chlorambucil plus rituximab. The Committee therefore concluded that the most plausible ICERs for idelalisib plus rituximab compared with fludarabine, cyclophosphamide and rituximab, chlorambucil plus rituximab and bendamustine plus rituximab were within the range of approximately £36,000 per QALY gained and £46,000 per QALY gained.

4.14 The Committee considered the most plausible ICER for idelalisib plus rituximab in people with previously treated refractory chronic lymphocytic leukaemia. The Committee was aware that in this group the relevant comparator was rituximab alone or best supportive care. The Committee recognised that the benefits for this group would probably be better than for the relapsed group given the paucity of other treatments. Nevertheless, the Committee explored the calculated cost-effectiveness for this group separately. It noted that in the company's proposed base-case analysis, after using the simple discount agreement price for idelalisib, the ICER was £26,400 per QALY gained for the comparison with rituximab alone and £35,300 per QALY gained for the comparison with best supportive care (see section 3.54). The Committee noted that if its preferred assumptions on intravenous immunoglobulin therapy usage were applied (see section 4.11), the ICER for the comparison with rituximab alone increased to £31,300 per QALY gained and for the comparison with best supportive care the ICER increased to £40,200 per QALY gained. The Committee was also aware that when its preferred assumption on treatment benefit of idelalisib plus rituximab following treatment discontinuation was applied (see section 4.10), the ICERs would likely increase further, up to a maximum of £41,000 per QALY gained for the comparison with rituximab alone and £50,000 per QALY gained for the comparison with best supportive care. The Committee concluded that the most plausible ICER for idelalisib plus

rituximab compared with rituximab alone is between approximately £31,000 per QALY gained and £41,000 per QALY gained, and the most plausible ICER for the comparison with best supportive care is between approximately £40,000 per QALY gained and £50,000 per QALY gained.

End-of-life considerations

4.15 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 of the economic modelling are plausible, objective and robust.

4.16 The Committee discussed each end-of-life criterion in turn for the populations that the company had provided evidence for (that is, people with previously treated high-risk relapsed and refractory chronic lymphocytic leukaemia). For the short life expectancy criterion, the Committee noted the results of Study 116 which showed that that mean overall survival in the rituximab plus placebo group was less than 24 months. The Committee then considered the mean overall survival for the comparators relevant to the high-risk relapsed group (disease relapse less than 24 months since previous treatment). It noted that the modelled mean overall survival for the comparators was less than 24 months (see section 3.31). The Committee further noted the clinical experts' view that life expectancy is approximately 12–24 months for people with high-risk relapsed disease and less than 12 months for people with refractory disease. The Committee therefore concluded that the short life expectancy

criterion was met for people with high-risk relapsed and refractory chronic lymphocytic leukaemia.

4.17 The Committee discussed the life extension criterion. For people with high-risk relapsed disease, the life expectancy was greater than 3 months with idelalisib plus rituximab (data supplied academic in confidence and so cannot be reported here) compared with the modelled mean overall survival for the relevant comparators (see section 3.31). For people with refractory chronic lymphocytic leukaemia, the mean overall survival with idelalisib plus rituximab in Study 116 demonstrated a life expectancy greater than 3 months compared with rituximab plus placebo (data supplied academic in confidence and so cannot be reported here). The Committee concluded that the life extension criterion was met for people with high-risk relapsed chronic lymphocytic leukaemia and for people with refractory chronic lymphocytic leukaemia.

4.18 The Committee discussed the evidence for the small population size. It noted evidence provided by the company which showed that fewer than 7000 people are likely to have idelalisib plus rituximab. The Committee also heard from the clinical experts that the number of people with previously treated chronic lymphocytic leukaemia is likely to be around 1400. The Committee concluded that both the relapsed and refractory chronic lymphocytic leukaemia groups fulfil the small population end-of-life criterion.

Innovation

4.19 The Committee discussed how innovative idelalisib plus rituximab is in its potential to make a significant and substantial impact on health-related benefits. It understood that idelalisib is a novel agent and that there was a high level of unmet need in this disease area, and it agreed that idelalisib offered a step change in the treatment of chronic lymphocytic leukaemia. Despite this, no additional evidence was submitted to suggest that these elements of innovation offered demonstrable and distinctive benefits of a substantial nature, which had not already been adequately captured in the QALY gain for idelalisib. The Committee concluded that no special considerations were needed to account for any health-related quality-of-life benefits that had not already been captured in the economic model.

Committee conclusions

4.20 The Committee considered its recommendations for the 4 relevant populations in turn (see section 4.3). In people with previously treated relapsed chronic lymphocytic leukaemia (that is, disease relapse 24 months or more after previous treatment), it noted that no evidence had been submitted to support making recommendations for this population. In the absence of evidence, the Committee concluded that idelalisib plus rituximab is not recommended as a cost-effective use of NHS resources for people with previously treated relapsed chronic lymphocytic leukaemia.

4.21 The Committee considered the use of idelalisib plus rituximab in people with previously treated high-risk relapsed chronic lymphocytic leukaemia (that is, disease relapse less than 24 months after previous treatment). The Committee noted that the most plausible ICERs for the comparisons with fludarabine, cyclophosphamide and rituximab, chlorambucil with rituximab and bendamustine with rituximab were within the range of £36,000 per QALY gained and £46,000 per QALY gained. It further noted that this population could be considered under the supplementary advice to the Committee on end-of-life treatments. The Committee therefore concluded that idelalisib plus rituximab represents a cost-effective use of NHS resources and should be recommended for people with previously treated high-risk relapsed chronic lymphocytic leukaemia.

4.22 The Committee considered the use of idelalisib plus rituximab in people with previously treated refractory chronic lymphocytic leukaemia (that is, treatment failure or disease relapse less than 6 months after previous treatment). The Committee noted that the most plausible ICER for the comparison with rituximab alone is between £31,000 per QALY gained and £41,000 per QALY gained and the most plausible ICER for the comparison with best supportive care is between £40,000 per QALY gained and £50,000 per QALY gained. It further noted that this population could be considered under the supplementary advice to the Committee on end-of-life treatments. The Committee therefore concluded that idelalisib plus rituximab represents a cost-effective use of NHS resources and should be recommended for people with previously treated refractory chronic lymphocytic leukaemia.

4.23 The Committee considered the use of idelalisib plus rituximab in people with untreated chronic lymphocytic leukaemia with a 17p deletion or TP53 mutation. It was aware that no cost-effectiveness evidence had been submitted for this group. The Committee recalled the comments it had received during the appraisal consultation, which highlighted that the potential benefits of idelalisib plus rituximab for this group were sizeable because of the poor prognosis associated with these types of genetic mutations. The Committee noted that this group would, in effect, have access to idelalisib if the disease became relapsed because of its conclusion in section 4.22 above; however, given the discussions with the clinical experts who advised that denying access to idelalisib plus rituximab in this group could be harmful (because chemotherapy is ineffective and increases the risk of further deletions and mutations), the Committee felt it was unreasonable to postpone access until their disease had relapsed. The Committee therefore concluded that idelalisib plus rituximab represents a cost-effective use of NHS resources and should be recommended for people with untreated chronic lymphocytic leukaemia with a 17p deletion or TP53 mutation.

Summary of Appraisal Committee's key conclusions

TA359	Appraisal title: Idelalisib for treating chronic lymphocytic leukaemia	Section
Key conclusion		
Idelalisib plus rituximab is not recommended as a cost-effective use of NHS resources for people with previously treated relapsed chronic lymphocytic leukaemia. The Committee noted that no evidence had been submitted to support making recommendations for this population.		4.20
Idelalisib plus rituximab is recommended as a cost-effective use of NHS resources for people with previously treated high-risk relapsed chronic lymphocytic leukaemia. The Committee noted that the most plausible incremental cost-effectiveness ratios (ICERs) were within the range of £36,000 per quality-adjusted life year (QALY) gained and £46,000 per QALY gained and this population could be considered under the supplementary advice to the Committee on end-of-life treatments.		4.21

Idelalisib plus rituximab is recommended as a cost-effective use of NHS resources for people with previously treated refractory chronic lymphocytic leukaemia. The Committee noted that the most plausible ICER for the comparison with rituximab alone is between £31,000 per QALY gained and £41,000 per QALY gained and the most plausible ICER for the comparison with best supportive care is between £40,000 per QALY gained and £50,000 per QALY gained. It further noted that this population could be considered under the supplementary advice to the Committee on end-of-life treatments.	4.22
Idelalisib plus rituximab is recommended as a cost-effective use of NHS resources for people with untreated chronic lymphocytic leukaemia with a 17p deletion or TP53 mutation. The Committee noted that this group would, in effect, have access to idelalisib if the disease became relapsed because of its conclusion in section 4.22. It further noted that because treatment with chemotherapy is potentially harmful for this type of disease, the Committee felt it was unreasonable to postpone access until their disease had relapsed.	4.23
Current practice	

Clinical need of patients, including the availability of alternative treatments	The Committee heard from the clinical experts that treatment options for disease which has been previously treated depends on the person's suitability for certain treatments, the treatments they have already had and the time since the last disease relapse. The clinical experts advised that re-treatment with fludarabine-based regimens (such as fludarabine, cyclophosphamide and rituximab) or alkylating agents (such as bendamustine plus rituximab or chlorambucil plus rituximab) is suitable for people whose disease has relapsed more than 24 months after their last treatment. The clinical experts noted that for people whose disease had relapsed less than 24 months after their last treatment, options are limited. Re-treatment is less effective and can cause the disease to develop deletions and mutations which in turn lead to chemotherapy-resistant chronic lymphocytic leukaemia. The Committee also discussed the clinical management of untreated chronic lymphocytic leukaemia in people with a 17p deletion or TP53 mutation. It heard from the clinical experts that people with this type of disease have very limited treatment options, which can include high-dose pulsed steroids with alemtuzumab. The Committee concluded that more treatment options are needed.	4.1
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee discussed how innovative idelalisib plus rituximab is in its potential to make a significant and substantial impact on health-related benefits. It understood that idelalisib is a novel agent, however the Committee concluded that no additional evidence had been submitted by the company to suggest the benefit of treatment with idelalisib had not already been taken into account in the QALY.	4.19

What is the position of the treatment in the pathway of care for the condition?	The marketing authorisation included people with chronic lymphocytic leukaemia whose disease had been previously treated and people with a 17p deletion or TP53 mutation whose disease is untreated. The Committee concluded that for the purposes of this appraisal, the following populations should be considered: • People whose disease has been previously treated and has relapsed more than 24 months after treatment. • People with high-risk relapsed disease whose disease has been previously treated and has relapsed less than 24 months after treatment. • People with refractory disease whose disease has failed treatment or relapsed less than 6 months after treatment. • Untreated disease with a 17p deletion of TP53 mutation.	2.1, 4.2
Adverse reactions	The summary of product characteristics lists the following adverse reactions to idelalisib, alone or with rituximab, as affecting more than 10% of patients: infections, neutropenia, diarrhoea, transaminase increase, rash, pyrexia and increased triglycerides. For full details of adverse reactions and contraindications, see the summary of product characteristics.	2.2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee considered the evidence submitted by the company. It noted that Study 116 included only those people with previously treated high-risk relapsed (relapse less than 24 months since previous treatment) or refractory chronic lymphocytic leukaemia.	4.5
	The Committee considered the evidence from Study 101-08 on the clinical effectiveness of idelalisib plus rituximab in people whose disease was untreated and who had a 17p deletion or TP53 mutation (see sections 3.14–3.18).	4.6

Relevance to general clinical practice in the NHS	The Committee noted that the baseline characteristics of patients in Study 116 represented a high-risk patient cohort who had taken an average of 3 prior therapies (see section 3.20). In addition, 43.2% of patients in the trial had a 17p deletion or TP53 mutation.	4.5
Uncertainties generated by the evidence	The Committee noted that the evidence from Study 101-08 was limited because it was based on a single-arm trial (Study 101-08) of 64 patients, only 9 of whom had a 17p deletion or TP53 mutation.	4.6
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee concluded that because no evidence had been submitted for people whose disease had relapsed more than 24 months after previous treatment, the results of Study 116 could not be used to inform its decision-making for this subgroup of people.	4.5
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The results of Study 116 showed a statistically significant improvement in median progression-free survival for idelalisib plus rituximab compared with rituximab plus placebo of 19.4 months (95% confidence interval [CI] 12.3, not reported) compared with 6.5 months (95% CI 4.0 to 7.3). The reported hazard ratio (HR) was 0.15 (95% CI 0.09 to 0.24, p=<0.001). The intention-to-treat analysis for median overall survival showed a statistically significant difference for idelalisib plus rituximab compared with rituximab plus placebo (HR 0.34, 95% CI 0.19 to 0.60, p=<0.001).	3.7
	The results of Study 101-08 showed at 36 months no patients with a 17p deletion or TP53 mutation had a progression event. Progression-free survival for the overall population at 36 months was 83%, compared with 100% for the 17p deletion or TP53 mutation patients. Overall survival at 36 months was 100% for the 17p deletion or TP53 mutation patients and 90% for the whole study population.	3.17
Evidence for cost effectiveness		

Availability and nature of evidence	The Committee considered the model presented by the company. It noted that the company had submitted an economic model which addressed the population in Study 116 – that is, people with previously treated chronic lymphocytic leukaemia which is high-risk relapsed or refractory.	4.8
	The Committee considered the company's rationale for not submitting an economic model for people with untreated disease and a 17p deletion or TP53 mutation. It heard from the company that due to the limited evidence base it was not possible to conduct an economic evaluation using the results of Study 101-08 (see section 3.22).	4.9
	It discussed the limitations of the available evidence base for the untreated population and concluded that an economic model could have been presented by the company. However, it noted that a proportion of patients in Study 116 had a TP53 mutation or 17p deletion (see section 4.5). It further noted the clinical expert's advice that in people with a 17p deletion or TP53 mutation, treatment with chemotherapy is ineffective and potentially harmful (see section 4.3). It therefore concluded that it would consider its recommendations for the untreated group in the light of its decision of the cost-effectiveness results from the company's model for the high-risk relapsed groups.	4.3, 4.5
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee heard from the Evidence Review Group (ERG) that the company's model contained an assumption that time on treatment was restricted, but that the benefits of treatment with idelalisib plus rituximab continued after both the time horizon of the trial and treatment discontinuation up to a maximum of 5 years. The Committee heard from the ERG that these assumptions may have overestimated the treatment effect of idelalisib plus rituximab.	4.10,

	The Committee heard from the ERG that the company had assumed in the proposed base case that 45% of patients whose disease did not respond to treatment would have intravenous immunoglobulin therapy (see section 3.58). It heard from the clinical experts that this was an overestimate and that in clinical practice, up to 20% of patients whose disease did not respond to therapy would have intravenous immunoglobulin therapy. The clinical experts also noted that intravenous immunoglobulin therapy is administered in up to 10% of patients whose disease did respond to treatment.	4.11
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee heard from the ERG that the company had used EQ-5D data collected alongside Study 116 for its pre-progression states and utilities from Dretzke et al. (2010) in its post-progression states. In the base case, patients who discontinued treatment with idelalisib plus rituximab maintained a permanently higher utility than those who were still having rituximab alone. Following the appraisal consultation the company submitted a proposed base case which used the EQ-5D trial data but corrected the errors identified by the ERG (see sections 3.51–3.56). The Committee heard from the ERG that these changes were appropriate (see section 3.58). The Committee therefore concluded that it was acceptable to use Study 116 EQ-5D data to inform the pre-progression utility values.	4.12
Are there specific groups of people for whom the technology is particularly cost effective?	In people with previously treated refractory chronic lymphocytic leukaemia the Committee recognised that the benefits for this group would probably be better than for the relapsed group given the paucity of other treatments.	4.14
What are the key drivers of cost effectiveness?	The Committee noted that the key drivers of cost effectiveness in the company model were the assumptions on the length of treatment benefit of idelalisib plus rituximab after treatment discontinuation and the proportions of people who have intravenous immunoglobulin therapy.	4.10, 4.11

Most likely cost-effectiveness estimate (given as an ICER)	The Committee concluded that the most plausible ICERs for idelalisib plus rituximab compared with fludarabine, cyclophosphamide and rituximab, chlorambucil plus rituximab and bendamustine plus rituximab were within the range of approximately £36,000 per QALY gained and £46,000 per QALY gained.	4.13,
	The Committee concluded that the most plausible ICER for idelalisib plus rituximab compared with rituximab alone is between approximately £31,000 per QALY gained and £41,000 per QALY gained, and the most plausible ICER for the comparison with best supportive care is between approximately £40,000 per QALY gained and £50,000 per QALY gained.	4.14
Additional factors taken into account		
Simple discount agreement	The company has a simple discount agreement that provides a discount to the list price of idelalisib. The level of the discount is commercial in confidence.	2.3
End-of-life considerations	The Committee concluded that the short life expectancy criterion was met for people with high-risk relapsed and refractory chronic lymphocytic leukaemia.	4.16, ,
	The Committee concluded that the life extension criterion was met for people with high-risk relapsed chronic lymphocytic leukaemia and for people with refractory chronic lymphocytic leukaemia.	4.17
	The Committee concluded that both the relapsed and refractory chronic lymphocytic leukaemia groups fulfil the small population end-of-life criterion.	4.18
Equalities considerations and social value judgements	No equalities issues were identified.	

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3 The company has arranged a simple discount agreement which provides a simple discount to the list price of idelalisib. The level of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the simple discount agreement should be directed to the company's customer service on +44 (0)203 681 4681 or at UKcustomer.services@gilead.com.

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

- Costing template and report to estimate the national and local savings and costs associated with implementation.
- A costing statement explaining the resource impact of this guidance.

6 Review of guidance

6.1 The guidance on this technology will be considered for review in September 2018. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
October 2015

7 Appraisal Committee members, guideline representatives and NICE project team

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 4 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 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.

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne
Vice Chair of Appraisal Committee C, Director of Public Health, City of Newcastle upon Tyne

Professor Kathryn Abel
Institute of Brain and Behaviour Mental Health, University of Manchester

Dr David Black
Medical Director, NHS South Yorkshire and Bassetlaw

Mr David Chandler
Lay member

Gail Coster
Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome
Honorary Professor, Dept of Primary Care and Population Health, University College London

Professor Rachel A Elliott
Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Nigel Langford
Consultant in Clinical Pharmacology and Therapeutics and Acute Physician, Leicester Royal Infirmary

Dr Andrea Manca
Health Economist and Senior Research Fellow, University of York

Dr Iain Miller
Founder and CEO, Health Strategies Group

Dr Paul Miller
Director, Payer Evidence, AstraZeneca UK

Professor Stephen O'Brien
Professor of Haematology, Newcastle University

Dr Claire Rothery
Research Fellow in Health Economics, University of York

Professor Peter Selby
Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Professor Matt Stevenson
Technical Director, School of Health and Related Research, University of Sheffield

Dr Paul Tappenden
Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

Professor Robert Walton
Clinical Professor of Primary Medical Care, Barts and The London School of Medicine & Dentistry

Dr Judith Wardle
Lay member

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager

Victoria Kelly
Technical Lead(s)

Dr Sally Doss and Joanne Holden
Technical Advisers

Lori Farrar
Project Manager

8 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Warwick Evidence:

- Kandala, N-B., Pink, J., Tsertsvadze, A., Sutcliffe, P., Court, R., Walewska, R., Clarke, A. Idelalisib Single Technology Appraisal – Idelalisib for relapsed chronic lymphocytic leukaemia [ID764]: A Single Technology Appraisal. Warwick Evidence, 2015

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 make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Gilead Sciences

II. Professional/expert and patient/carer groups:

- Chronic Lymphocytic Leukaemia Support Association
- Leukaemia CARE
- Lymphoma Association
- Association of Cancer Physicians
- Cancer Research UK
- Royal College of Pathologists
- Royal College of Physicians
- Royal College of Radiologists

III. Other consultees:

- Department of Health
- NHS England

- Welsh Government

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

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- GlaxoSmithKline (chlorambucil, ofatumumab)
- Roche Products (rituximab, obinutuzumab)
- National Cancer Research Institute
- Warwick evidence
- National Institute for Health Research Health Technology Assessment Programme

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on Idelalisib for previously treated chronic lymphocytic leukaemia by attending the initial Committee discussion and providing a written statement to the Committee. They are invited to comment on the ACD.

- Professor Christopher Fegan, Director of Research and Development, nominated by Gilead – clinical expert
- Dr Francesco Forconi, Consultant and Associate Professor, nominated by Royal College of Physicians – clinical expert
- Nick York, Nominated by CLL Support Association – patient expert
- Trisha Gardom, CLL Patient Advocate, nominated by CLL Support Association – patient expert

D. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Gilead

About this guidance

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

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

We have produced information for the public explaining this guidance. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

NICE produces guidance, standards and information on commissioning and providing high-quality healthcare, social care, and public health services. We have agreements to provide certain NICE services to Wales, Scotland and Northern Ireland. Decisions on how NICE guidance and other products apply in those countries are made by ministers in the Welsh government, Scottish government, and Northern Ireland Executive. NICE guidance or other products may include references to organisations or people responsible for commissioning or providing care that may be relevant only to England.

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 have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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