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Full title: Ibrutinib for treating Waldenström's macroglobulinaemia: An Evidence Review Group Perspective of a NICE Single Technology Appraisal

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Running header: ERG review of ibrutinib for Waldenström's macroglobulinaemia

Abstract

As part of its Single Technology Appraisal (STA) process, the UK National Institute for Health and Care Excellence (NICE) invited the manufacturer of ibrutinib (Janssen) to submit evidence on the clinical effectiveness and cost-effectiveness of ibrutinib for treating Waldenström's macroglobulinaemia (WM). The School of Health and Related Research Technology Assessment Group at the University of Sheffield was commissioned to act as the independent Evidence Review Group (ERG). The ERG produced a critical review of the evidence for the clinical effectiveness and cost-effectiveness of ibrutinib based on the company's submission to NICE. The clinical evidence was derived from one Phase II, single-arm, open-label study of ibrutinib in adult patients with WM who had received at least one prior therapy (Study 1118E) and an indirect comparison using a matched cohort from a retrospective European Chart Review of patients receiving various treatments for WM. The indirect comparison suggested a hazard ratio for progression-free survival (PFS) of 0.25 (95% confidence interval 0.11 to 0.57). The ERG had concerns regarding the high risk of bias in Study 1118E, the limited generalisability of the study and the absence of RCT evidence. The company's Markov model assessed the cost-effectiveness of ibrutinib versus rituximab/chemotherapy for patients with relapsed/refractory (R/R) WM from the perspective of the National Health Service (NHS) and Personal Social Services (PSS) over a lifetime horizon. Based on the company's original Patient Access Scheme (PAS), the company's probabilistic model generated an incremental cost-effectiveness ratio (ICER) for ibrutinib versus rituximab/chemotherapy of £58,905 per quality-adjusted life-year (QALY) gained. Following a critique of the model, the ERG's preferred analysis, which corrected cost errors and used the observed mortality rate from Study 1118E, generated a probabilistic ICER of £61,219 per QALY gained; based on this amended model, additional exploratory analyses produced ICERs for ibrutinib which were greater than £60,000 per QALY gained. Subsequently, the company offered to provide ibrutinib at a price that resulted in ibrutinib being cost-effective within the Cancer Drugs Fund (CDF). The Committee recommended ibrutinib for use in the CDF as an option for treating WM in adults who have had at least one prior therapy, only if the conditions in the managed access agreement for ibrutinib are followed.

Key messages for decision-makers

- The main clinical evidence for ibrutinib was Study 1118E – a single-arm, open-label study of ibrutinib in adult patients with Waldenström's macroglobulinaemia (WM) who had received at least one prior therapy, and an indirect comparison using a matched cohort from a retrospective European Chart Review of patients receiving various treatments for WM. The indirect comparison suggested a hazard ratio (HR) for progression-free survival (PFS) of 0.25 (95% confidence interval 0.11 to 0.57). No comparative analysis was undertaken for survival outcomes.
- The main issues identified by the ERG included: (i) the high risk of bias in Study 1118E; (ii) concerns regarding the generalisability of Study 1118E; (iii) the absence of RCT evidence; (iv) uncertainty surrounding the company's indirect comparison for PFS; (v) the absence of an indirect comparison of overall survival and (vi) concerns regarding the structure of the company's model and the evidence used to inform its parameters.
- Additional analyses undertaken by the ERG suggested that the incremental cost-effectiveness ratio (ICER) for ibrutinib versus rituximab/chemotherapy was expected to be greater than £60,000 per quality-adjusted life year (QALY) gained (using the original Patient Access Scheme [PAS]). The ERG's analyses showed that even under favourable assumptions, varying the HR for PFS between 0.01 and 1.00 produced ICERs for ibrutinib versus rituximab/chemotherapy of at least £56,917 per QALY gained.
- Based on additional analyses and an updated PAS, the appraisal committee concluded that the most plausible ICER was likely to be at least £54,100 per QALY gained. The company subsequently offered an improved value proposition for ibrutinib for use in the Cancer Drugs Fund (CDF).
- Ibrutinib was recommended, within its marketing authorisation, for use in the CDF as an option for treating WM in adults who have had at least one prior therapy, only if the conditions in the managed access agreement for ibrutinib are followed.

1. INTRODUCTION

Health technologies must be shown to be clinically effective and to represent a cost-effective use of resources to be recommended for use within the National Health Service (NHS) in England. The National Institute for Health and Care Excellence (NICE) is an independent organisation responsible for providing national guidance on promoting good health, and preventing and treating ill health, in priority areas with significant impact. The NICE Single Technology Appraisal (STA) process usually covers new technologies soon after they have received UK marketing authorisation and is specifically designed for the appraisal of a single health technology within a single indication [1]. Within the STA process, the manufacturer of a technology provides NICE with a written submission containing relevant clinical effectiveness evidence alongside a health economic model that summarises the company's estimates of the cost-effectiveness of the technology. The Evidence Review Group (ERG), an external academic organisation which is independent of NICE, reviews the submission with advice from clinical specialists and produces an ERG report. The NICE appraisal committee (AC) considers the company's submission (CS), the ERG report, and testimony from experts and other stakeholders and formulates preliminary guidance - the appraisal consultation document (ACD) - which indicates the initial decision of the AC regarding the recommendation (or not) of the intervention. Stakeholders are subsequently invited to comment on the submitted evidence and the ACD, after which an ACD may be produced or a final appraisal determination (FAD) issued, which is open to appeal. An ACD is not produced when the intervention is recommended without restriction; in such instances, a FAD is produced directly. This paper presents a summary of the ERG report [2] produced by the School of Health and Related Research Technology Assessment Group at the University of Sheffield and the NICE FAD [3] for the STA of ibrutinib for the treatment of Waldenström's macroglobulinaemia (WM). It also covers the subsequent development of the NICE guidance for the use of this drug in England [4]. Full details of all relevant appraisal documents can be found on the NICE website [5].

2. DECISION PROBLEM

WM is an incurable lymphoproliferative B-cell disorder characterised by infiltration of lymphoplasmacytic cells into the bone marrow and immunoglobulin M (IgM) monoclonal gammopathy [6]. WM is considered to be a lymphoplasmacytic lymphoma (LPL) by both the Revised European American Lymphoma (REAL) and World Health Organization (WHO) classification systems. WM is rare and accounts for less than 2% of all non-Hodgkin's Lymphomas (NHLs) [6]. Current estimates from the British Committee for Standards in Haematology (BCSH) suggest an incidence rate for WM of 0.55 per 100,000 people per year in the UK, which corresponds to approximately 292 new cases in England each year.

Diagnosis requires demonstration of an IgM monoclonal protein and histological evidence of bone marrow infiltration by lymphoplasmacytic cells. Several factors are associated with poor prognosis,

including: (i) advanced age (>65 years); (ii) β2-microglobulin >3mg/L; (iii) anaemia (haemoglobin ≤11.5g/dL); thrombocytopenia (platelet count ≤100 x 109/L) and (iv) IgM monoclonal gammopathy (IgM >7.0g/dL) [6]. Based on the International Prognostic Scoring System for WM (IPSSWM) for newly diagnosed patients, median survival is estimated to be 11.88 years for low-risk patients, 8.22 years for intermediate-risk patients and 3.63 years for high-risk patients [7].

Clinical manifestations of WM include cytopenias (anaemia) and lymphadenomegaly resulting from infiltration by lymphoplasmacytic cells and IgM paraprotein-related symptoms such as: cryoglobulinemia; cold agglutinin syndrome; demyelinating neuropathy; amyloidosis (involving kidneys, the heart and the nervous system); infections, and; symptomatic hyperviscosity (visual disturbance, headache, dizziness, altered consciousness, fatigue and weakness) [6]. There is no evidence relating to the impact of WM and its treatment on health-related quality of life (HRQoL); unpublished patient survey data suggest that the symptoms which impact most on patients' HRQoL are: tiredness or lack of energy; weakness; frequent infections; tingling or numbness in the feet or legs and shortness of breath [8].

2.1 Current treatment

There is currently no licensed treatment that represents the standard of care for WM. Taking into account the fitness of the patient, standard treatment is typically based on treatment options developed for other lymphoproliferative diseases including multiple myeloma (MM) and chronic lymphocytic leukaemia (CLL). WM treatment guidelines have been published by the BCSH and the European Society for Medical Oncology (ESMO) [9, 10]. Both guidelines recognise the lack of randomised evidence for WM treatments, especially as part of combination therapy. For first-line treatment of medically fit patients, both guidelines advocate rituximab in combination with chemotherapy, with the deferral of rituximab in cases of "IgM flare". Both guidelines reject the use of rituximab as maintenance therapy due to limited evidence. For medically fit patients with relapsed or refractory (R/R) disease, guidelines advocate continuing with rituximab and chemotherapy combination therapy, albeit using a different regimen from that given as first-line treatment [9, 10]. For many patients of advancing age and frailty there are very few effective options, particularly for those with R/R disease.

In October 2015, NICE issued a final scope to appraise the clinical effectiveness and cost-effectiveness of ibrutinib for WM [11]. The NICE scope defined two discrete populations: (i) adults with WM who have received at least one prior therapy; (ii) adults with WM who have not received prior therapy and for whom chemo-immunotherapy is unsuitable. The comparators for ibrutinib within the previously treated population included rituximab in combination with chemotherapy (various regimens), and cladribine, chlorambucil and rituximab as monotherapies. For the untreated population in whom chemo-

immunotherapy is unsuitable, the comparators included rituximab monotherapy, chlorambucil monotherapy and best supportive care (BSC).

3. Independent ERG review

The company (Janssen) provided a submission to NICE on the clinical effectiveness and cost effectiveness of ibrutinib for treating WM [8]. This submission was critically appraised by the ERG. Subsequently, the ERG identified areas requiring clarification, for which the company provided additional evidence prior to completion of the ERG report [12].

3.1 Clinical evidence submitted by the company

The CS identified one relevant single-arm study – Study 1118E [13]. In Study 1118E, 63 previously-treated adult patients with WM from three sites in the USA were allocated to receive ibrutinib at a dose of 420mg/day. Treatment was administered for a median of 19.1 months (range 0.5 to 29.7 months) and 43/63 patients (68%) remained on treatment after the final data cut-off (DCO) of 19th December 2014. The median age was 63.0 years (mean age = 64.5 years). Most (76.2%) patients were male. Median time from diagnosis of WM to study entry was 76 months (range: 6 to 340 months). The median number of prior regimens was 2 (range: 1 to 9 regimens).

The principal efficacy outcomes were response and progression-free survival (PFS). The reported overall response rate (ORR, any response) was 90.5% (95% confidence interval [CI] 80.4% to 96.4%), which was achieved by 57/63 patients. Responders were categorised as follows: very good partial response (VGPR): n=10; partial response (PR): n=36; and minor response: n=11. The major response rate (defined as PR or better) was 73% (95% CI 60.3% to 83.4%). Based on data from the clinical study report (CSR), the Kaplan-Meier estimate for the event-free rate for all responders at 18 months was 80.9% (95% CI 64.9% to 90.2%), and the corresponding estimate for major responders was 86.7% (95% CI 67.9% to 94.9%) [14]. The CS reported that subgroup analyses of ORR and major response rate were consistent across most subgroups (e.g. by age, Eastern Cooperative Oncology Group [ECOG] score at baseline, IPSSWM risk score) [8]. The Kaplan-Meier estimate of the PFS probability at 24 months was 69.1% (95% CI 53.2% to 80.5%). At the 19th December 2014 DCO, 60 of the 63 patients were still alive and the estimated OS probability was 95.2% (95% CI 86% to 98.4%). Treatment with ibrutinib resulted in a significant decline in median percentage of bone marrow infiltration from 60% to 25% ($p<0.001$). There was insufficient evidence of a correlation between serum IgM levels and bone marrow involvement at 6 months ($r=0.03$, $p=0.83$), but there was evidence at 12 months ($r=0.51$, $p<0.001$) and at 24 months ($r=0.56$, $p<0.008$). At baseline, adenopathy and splenomegaly were identified by computed tomography (CT) in 37/63 (59%) and 7/63 (11%) patients, respectively, and the number of patients with lymphadenopathy and splenomegaly were reduced after ibrutinib treatment.

Given the absence of randomised head-to-head evidence comparing ibrutinib versus any other WM treatment, the CS presented an indirect comparison using PFS data from Study 1118E [13] and a matched cohort from a retrospective European Chart Review (ECR) [15]. The company's multivariable Cox model produced an estimated hazard ratio (HR) for PFS for ibrutinib versus standard therapies of 0.25 (95% CI 0.11 to 0.57). The use of alternative imputation methods produced more favourable HRs for PFS ranging from 0.19 to 0.22.

The CS reported safety data from Study 1118E [13] together with additional results from selected supplementary studies in which patients with CLL or mantle cell lymphoma (MCL) received ibrutinib [16-20]. Within Study 1118E and the supplementary studies, the majority of adverse events (AEs) were mild to moderate in severity. The incidence of Grade 3/4 AEs was 49% in Study 1118E. The discontinuation rate following a median treatment duration of 19.1 months was 9.5%.

The CS identified one ongoing study of ibrutinib in WM - PCYC-1127-CA (iNNOVATE - ClinicalTrials.gov Identifier NCT02165397). This is an international multi-centre, Phase III trial evaluating the safety and efficacy of ibrutinib in combination with rituximab in patients with WM, which includes a third arm of ibrutinib monotherapy, an open-label sub-study for 31 patients who are refractory to rituximab. Results from this study were not available at the time of the appraisal; the estimated study completion date is January 2019.

3.2 Critique of clinical effectiveness evidence and interpretation

The ERG considered the company's reviews of clinical efficacy and safety evidence to be poorly reported and noted a lack of high quality evidence. There were no randomised controlled trials (RCTs) or non-randomised controlled trials of ibrutinib in the relevant populations listed in the NICE scope [11]. The clinical evidence consisted of one Phase II, single-arm, open-label study of ibrutinib in adult patients with WM who had received at least one prior therapy [13]. No evidence was available for ibrutinib in treatment-naïve patients with WM who are unsuitable for chemo-immunotherapy.

The ERG noted several concerns regarding Study 1118E [13]. Whilst the study was generally well-reported, it was at high risk of selection, performance and other bias, not only on account of its study design but also because of inadequate reporting of outcome measurement. The study included only 63 patients, who were generally younger and had less severe disease than the R/R adults with WM who might routinely present in practice in England. The outcome measures used were generally valid and reliable but the response criteria (the primary outcome) were "modified" from international standards [21]. With the exception of complete response (CR), the definitions of minor response, PR and VGPR applied in Study 1118E, as reported in the CS and protocols, differed from internationally recognised response criteria: in Study 1118E, they are limited to serum IgM level only, whilst international

standards also require the presence or absence of clinically significant findings or symptoms. The ERG noted that IgM response alone is insufficient as an outcome for WM because clinical benefit might be seen in patients without IgM response, or IgM reduction might not see an improvement of symptoms. Whilst response rates were consistent across most subgroups, differences in major response were particularly apparent for patients with different levels of ß$_2$–microglobulin, haemoglobin, bone marrow disease involvement and genotype MYD88^{L265P} and CXCR4^{WT}.

The ERG noted that AEs of any grade were very frequent in all studies included in the CS, with up to 100% of patients in any of the included studies experiencing at least one AE and between 42% and 57% experiencing the most frequent event - diarrhoea [8].

The ERG also had concerns regarding the reliability of the company's indirect comparison, in particular due to: (i) the potential for unadjusted confounders; (ii) the lack of a unique matched sample from the ECR [15] and (iii) the exclusion of patients who had received five or more prior lines of treatment. In addition, the CS did not include an analysis of the relative survival impact of ibrutinib versus standard therapies for WM.

3.3 Cost-effectiveness evidence submitted by the company

The company's health economic model adopted a sequence-based Markov approach to estimate the health outcomes and costs for ibrutinib versus rituximab/chemotherapy for patients with R/R WM from the perspective of the NHS and Personal Social Services (PSS) over a 30-year (lifetime) horizon. The model included five health states: (1) second-line progression-free; (2) third-line progression-free; (3) fourth-line progression-free; (4) BSC and (5) dead. The model used parametric curves fitted to data on PFS, time to progression, pre-progression mortality and post-progression survival to inform transition rates between the health states. Transitions between states were modelled using a 28-day cycle length. Patients entered the model in the second-line progression-free state and received treatment with ibrutinib or rituximab/chemotherapy. Within the ibrutinib group, the probability of being progression-free at any time t was modelled using a parametric (Weibull) survivor function fitted to the PFS time-to-event data from Study 1118E [13]. Within the ibrutinib group, the probability that a patient leaving the second-line progression-free state dies was modelled using age- and sex-adjusted general population mortality hazards derived from life tables [22]. Within the rituximab/chemotherapy group, PFS in second-line was modelled using the inverse of the HR derived from the multivariable Cox model applied to the ibrutinib PFS curve [8], whilst the probability that a patient leaving the second-line progression-free state dies was modelled using data derived from the matched ECR cohort [15]. Within both treatment groups, progression events in the third- and fourth-line progression-free states were estimated using data from the ECR for patients who were starting fourth-line treatment, whilst the probability of death in all post-second-line progression-free states was based on data from the ECR for patients who

had progressed from third-line treatment. A proportion of patients were assumed to transit directly to BSC after progressing from each line of therapy. HRQoL was differentiated according to the presence/absence of disease progression; owing to a lack of evidence, health utilities were based on EQ-5D-5L data collected within the RESONATE study of ibrutinib in R/R CLL and other literature [23]. Disutilities associated with AEs were included only for second-line treatment, based on published health valuation studies relating to CLL states [23, 24] and additional assumptions [8]; AEs associated with subsequent-line treatments were not included in the model. The model included costs associated with: (i) drug acquisition; (ii) drug administration (applied to the rituximab/chemotherapy regimens only); (iii) routine follow-up; (iv) the management of AEs; (v) BSC and (vi) terminal care. Resource use and cost estimates were drawn from the British National Formulary (BNF) [25], NHS Reference Costs 2014/15 [26], published literature [27] and expert opinion [8]. The company's analysis included a Patient Access Scheme (PAS) for ibrutinib which took the form of a simple price discount. The value of this discount changed throughout the course of the appraisal. The level of the PAS is confidential; all cost-effectiveness results presented here are based on the original PAS.

Based on a re-run of the probabilistic version of the company's base case model by the ERG, the incremental cost-effectiveness ratio (ICER) for ibrutinib (including the original PAS) versus rituximab/chemotherapy was expected to be £58,905 per quality-adjusted life year (QALY) gained (deterministic ICER = £58,630 per QALY gained). Assuming a willingness-to-pay (WTP) threshold of £30,000 per QALY gained, the company's base case model suggested that the probability that ibrutinib produces more net benefit than rituximab/chemotherapy was approximately zero. Within the company's deterministic sensitivity analyses (DSAs) and scenario analyses, the ICER for ibrutinib versus rituximab/chemotherapy was consistently greater than £47,000 per QALY gained. The CS did not make a case that ibrutinib satisfies NICE's End of Life criteria, but did request that ibrutinib be listed on the Cancer Drugs Fund (CDF) within the WM indication.

3.3.1 Critique of cost-effectiveness evidence and interpretation

The ERG critically appraised the company's economic analysis and partially double-programmed the company's model. The main issues identified by the ERG are discussed below; the full critique can be found in the ERG report and the accompanying addendum [2, 28].

3.3.1.1 Absence of any economic analysis of ibrutinib in the first-line (treatment-naïve) setting

The company's model related to patients who have received previous treatment for WM. The company did not present any evidence relating to the clinical effectiveness or cost-effectiveness of ibrutinib in treatment-naïve patients for whom chemo-immunotherapy is unsuitable. Therefore, the scope of the economic analysis was narrower than the marketing authorisation for ibrutinib in the WM indication.

3.3.1.2 *Concerns regarding the company's modelling approach*

(i) Disconnect between the evidence and the model

The company's model structure included three progression-free health states in which active treatment was assumed to be used (second-, third- and fourth-line therapy). All patients entered the model in the second-line progression-free state. However, this is inconsistent with the evidence used to inform the baseline PFS curve for ibrutinib and the evidence used to inform the indirect comparison. Within the subset of patients from Study 1118E who were included in the company's matching exercise used to generate the treatment effect for ibrutinib (n=47), the majority of patients had received two or more prior lines of therapy (up to a maximum of four prior lines) [8]. Similarly, the matched cohort from the ECR (n=175) had received a median of two prior lines of therapy (range 1-4 lines). Consequently, the baseline risk of PFS and the treatment effects estimated from the Cox model do not correspond to the model's second-line progression-free health state. Whilst the way that this evidence was used in the model implies that the number of prior lines of therapy received is not a treatment effect modifier, the progression rates for the third- and fourth-line progression-free health states applied in the model differed from those used for second-line progression-free health state. The ERG also noted that the evidence used to inform progression and death event rates throughout the subsequent states of the model was inconsistent with the definition of modelled health states (see Table 1).

Table 1: Summary of evidence used to inform progression and death event rates by line of therapy

[INSERT TABLE 1 HERE]

(ii) Approach to modelling competing risks of progression and pre-progression death

Pre-progression mortality in the second-line progression-free state was modelled conditional on PFS: the PFS curve determines the probability of leaving the state, whilst the pre-progression mortality curve determines the proportion of those patients leaving the state who transit to the dead state. This meant that within the ibrutinib group, the estimated contribution of PFS to overall survival would always be the same irrespective of the pre-progression mortality rate assumed in that state. As such, the pre-progression mortality curve was entirely independent of survival gains accrued in the second-line progression-free state and impacted only upon survival gains accrued in subsequent-line states. This approach does not appropriately consider competing risks of progression and death and meant that changing these input parameters produced counter-intuitive model results. Given the underlying Markov structure adopted within the model, the ERG considered that the most appropriate approach would involve the independent modelling of time to progression (censoring for death) and pre-progression mortality (censoring for progression) in order to properly account for competing risks. However, this would have required the re-estimation of treatment effects on progression and/or pre-progression death separately.

(iii) Structural assumption of constant mortality hazard in third- and fourth-line progression-free states
The company's Markov approach imposed a structural assumption whereby survival following progression on second-line treatment must follow an exponential distribution. This was due to the use of multiple intermediate health states within the company's model (third-line progression-free, fourth-line progression-free and BSC). Whilst it would have been possible to apply time-variant event rates through the use of a semi-Markov design (using multiple tunnel states for incident patients entering each intermediate state during each cycle), or through the use of patient-level simulation, this was not possible within the company's implemented model. In response to a request for clarification from the ERG, the company provided additional analyses of pre-progression mortality data for patients receiving third-/fourth-line treatment; these analyses indicated that the exponential function provided a worse fit relative to the other models assessed.

3.3.1.3 Potentially inappropriate data used to inform pre-progression mortality for rituximab/chemotherapy

Given its structure, the model should have used a pre-progression mortality function, whereby only deaths occurring prior to progression are counted as events, and deaths occurring after progression are censored. The ERG had concerns that the data from the ECR [15], which were used to model pre-progression mortality for the rituximab/chemotherapy group, may actually reflect overall survival (including all deaths). This concern was raised because the relevant figure in the CS was labelled "Time to Death" [8]. Following the clarification process, the company stated that the figure contained in the CS reflected pre-progression mortality and also provided the Kaplan-Meier curve for OS from the ECR [15]. However, the two curves appeared to reflect the same data; this suggested that either the CS or the company's clarification response was inaccurate; hence, it remains unclear whether the model uses data on all deaths or only those occurring before progression to model pre-progression mortality for the rituximab/chemotherapy group. If OS data were used in the model in error, mortality in the comparator group would be artificially inflated and the ICER for ibrutinib could be significantly higher than the model suggested.

3.3.1.4 Questionable assumption of general population mortality rates for ibrutinib patients in the second-line progression-free state

The company's model assumed that pre-progression mortality for patients receiving ibrutinib reflected mortality rates in the general population; this assumption was made because only three patients died within the 24-month follow-up period within Study 1118E [13]. The ERG noted that the observed death rate within Study 1118E is higher than that for the age- and sex-matched general population. This suggests that the company's model underestimates the pre-progression mortality rate for the ibrutinib group.

3.3.1.5 Limited clinical evidence available for ibrutinib versus rituximab/chemotherapy

The ERG highlighted that there is an absence of head-to-head RCTs comparing ibrutinib versus any other therapy, and that the company's adjusted arm-based indirect comparison is subject to weaknesses and uncertainties. In addition, Study 1118E recruited only a small patient population (n=63) and the analysis at DCO 19th December 2014 included only three deaths, all of which occurred prior to disease progression. Furthermore, Study 1118E did not include the use of a preference-based measure of HRQoL and no other HRQoL studies in WM were identified from the literature. As a consequence of these issues, the ERG considered that any estimate of the relative benefits of ibrutinib on PFS, OS and HRQoL should be considered highly uncertain and that the results of the company's economic analysis were largely speculative.

3.3.1.6 Additional concerns

The ERG identified several additional issues regarding the company's model; these related to: (i) the company's parametric survival modelling and model selection procedures; (ii) the use of separate evidence sources to inform the health gains and costs associated with rituximab/chemotherapy; (iii) the use of a blended comparator; (iv) concerns regarding health utilities assumed within the model; (v) errors and discrepancies relating to drug acquisition costs for rituximab/chemotherapy, and (vi) the incomplete representation of uncertainty. These issues are discussed in detail in the ERG report [2].

3.4 Additional work undertaken by the ERG

The ERG undertook 10 sets of exploratory analyses. These analyses explored the impact of correcting the drug acquisition and follow-up costs, the use of alternative PFS treatment effect estimates, the use of observed pre-progression mortality rates for ibrutinib from Study 1118E, the removal of all assumed survival gains, the use of a Weibull distribution for pre-progression mortality in the rituximab/chemotherapy group, and the use of alternative utility values for the BSC state. In addition, the ERG undertook a threshold analysis in which the HR for PFS was varied from 0.01 to 1.0. The ERG's preferred analysis included the re-estimation of drug acquisition costs, the correction of errors in the follow-up costs and the use of observed pre-progression mortality data from Study 1118E. This analysis generated a probabilistic ICER of £61,219 per QALY gained (Table 2). Based on this ERG-preferred model, the subsequent exploratory analyses produced ICERs for ibrutinib which were greater than £60,000 per QALY gained. The most extreme scenario, which assumed no additional survival gain for ibrutinib, produced an ICER of £390,432 per QALY gained. The ERG's threshold analysis suggested that irrespective of the HR for PFS, the ICER for ibrutinib versus rituximab/chemotherapy was at least £56,917 per QALY gained (Figure 1).

Table 2: Summary of key results from the CS and the ERG report (using the original PAS for ibrutinib in the WM indication)

[INSERT TABLE 2 HERE]

Figure 1: ERG exploratory analysis 10 - threshold analysis around HR for PFS (using the original PAS for ibrutinib in the WM indication)

[INSERT FIGURE 1 HERE]

3.5 Conclusion of the ERG report

The absence of any head-to-head RCT evidence for ibrutinib versus standard therapies and concerns regarding the company's adjusted arm-based indirect comparison result in considerable uncertainty surrounding the clinical benefits of ibrutinib for the treatment of WM. Given the weaknesses in the company's model and the evidence used to inform it, the true ICER for ibrutinib versus rituximab/chemotherapy remains unclear. Notwithstanding this uncertainty, ERG's exploratory threshold analyses suggested that even under the company's optimistic assumption of general population mortality rates whilst patients are receiving ibrutinib, the ICER for ibrutinib versus rituximab is not expected to be below £56,917 per QALY gained, irrespective of the HR for PFS. Other things being equal, this represents a best-case scenario for the cost-effectiveness of ibrutinib versus rituximab/chemotherapy in the R/R WM setting. Given the highly favourable assumptions regarding OS benefits employed in the company's model, the ERG considered it unlikely that further data collection on PFS and OS outcomes for patients receiving ibrutinib would lead to more favourable cost-effectiveness estimates.

4. Methodological issues

The principal uncertainty relates to the absence of any head-to-head randomised evidence through which to estimate the benefits of ibrutinib on clinically meaningful outcomes, and the potential for bias and confounding in the company's indirect comparison of PFS outcomes. Alongside these clinical uncertainties, the company's model was subject to structural and implementation issues which limit the reliability of the results.

5. National Institute for Health and Care Excellence (NICE) guidance

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

The ACD (published October 2016) stated that ibrutinib was not recommended within its marketing authorisation for treating WM in adults who have had at least one prior therapy or as first-line treatment when chemo-immunotherapy is unsuitable. The AC noted that the company's base case ICER was well above the level which could be accepted as a cost-effective use of NHS resources, and that whilst the company had requested that ibrutinib be referred to the CDF, it did not have the plausible potential for satisfying the criteria for routine use.

In response to the ACD, the company submitted a revised version of the model which included five amendments:

(1) The survivor function for PFS for the ibrutinib group was replaced with data relating to the 12th December 2014 DCO of Study 1118E.
(2) Pre-progression mortality in the ibrutinib group was modelled using an exponential survivor function derived from Study 1118E, which was capped at the level of general population mortality.
(3) Pre-progression mortality in the rituximab/chemotherapy group was modelled using an alternative survivor function derived from a re-analysis of the ECR.
(4) Chemotherapy drug cost calculations were amended.
(5) The PAS for ibrutinib was updated.

The ERG noted that the company's revised model did not address all of the issues raised within the ERG report [2]. Despite the company providing additional explanation, the ERG remained unclear whether the pre-progression mortality function in the rituximab/chemotherapy group had been generated appropriately and noted that this aspect of the model had the propensity to dramatically increase the ICER for ibrutinib versus rituximab/chemotherapy, as previously shown in the ERG's exploratory analyses.

Following the second AC meeting, the company proposed an improved commercial offer for the use of ibrutinib in the WM indication in the CDF. In September 2017, NICE published its FAD, which made the following recommendation: *"*Ibrutinib is recommended, within its marketing authorisation, for use in the CDF as an option for treating *Waldenström's* macroglobulinaemia in adults who have had at least 1 prior therapy or as first-line treatment when chemo-immunotherapy is unsuitable, only if the conditions in the managed access agreement for ibrutinib are followed*"* [3].

5.1 Consideration of clinical effectiveness and cost-effectiveness issues

This section discusses the key issues considered by the AC. The full list can be found in the FAD [3].

5.1.1 Clinical trial evidence

The committee noted that the clinical evidence for ibrutinib came from one single-arm, open-label study and that Study 1118E was generally well reported. The committee noted that there were several potential biases resulting from the use of an open-label study design. The committee concluded that Study 1118E is of a reasonable quality, is generalisable to UK clinical practice and is suitable for decision-making, but is limited by the lack of a comparison against a treatment used in the UK. The AC concluded that the longer-term effects of ibrutinib on progression and survival are uncertain because no data are available. The committee understood that no clinical trial evidence had been presented for WM in adults who have not had prior therapy and for whom chemo-immunotherapy is unsuitable.

5.1.2 Indirect comparison

The committee understood that the company's indirect comparison suggested a substantial reduction in the risk of disease progression with ibrutinib compared with existing WM therapies. The committee was aware that the ERG had several concerns with the company's approach, including the methods used to select patients in the matched cohort. Based on the results of the indirect comparison and the testimonies from patients and clinical experts, the committee accepted that ibrutinib appears to be more clinically effective than existing treatments, but concluded that there is considerable uncertainty about the size of the long-term benefit because of limitations in the available data.

5.1.3 Company's economic model structure

The committee noted that the company had developed a Markov model comparing ibrutinib with treatment of physician's choice for patients with R/R WM who had had one prior therapy. The committee heard from the ERG that many patients in Study 1118E had more than one prior therapy and that the sequencing used in the company's model was inconsistent with the data and population in the clinical study. The committee concluded that the model structure was acceptable for decision-making but was mindful of its limitations.

5.1.4 Uncertainties around plausibility of assumptions and inputs in the economic model

The committee considered the estimates of pre-progression mortality and accepted that there is uncertainty because of limitations in the data available. The committee noted the ERG's comments that the company had potentially used unsuitable data to inform the pre-progression mortality for the comparator group. The committee noted that, in response to consultation, the company had revised its approach to modelling pre-progression mortality for the comparator group but the committee heard from the ERG that some uncertainty remained about whether there was an inflated risk of death prior to progression in the comparator group. However, the committee noted that the cost-effectiveness estimates were not sensitive to changes in pre-progression mortality for the comparator group and concluded that the company's revised approach was acceptable for decision-making (although the ERG

notes that the true impact of this issue remains unclear due to ongoing ambiguity regarding which data were used to model pre-progression mortality).

The committee noted that the company's original model had assumed general population mortality rates for pre-progression mortality in ibrutinib arm. The committee was aware that the company had revised its modelling approach, in response to the ERG's concerns reported in the ACD, to assume a constant hazard based on Study 1118E data until the constant hazard crossed the general population hazard, when the general population hazard was assumed. The committee concluded that the company's approach was likely to represent a 'best case' scenario and that a less favourable mortality rate would lead to a higher ICER than the one presented in the company's base case.

5.1.5 Most plausible ICER

The committee noted that the company's base-case ICER incorporating the updated PAS for ibrutinib and revisions to the model was £54,100 per QALY gained. The committee recalled its earlier conclusions that there is uncertainty about the size of the clinical benefit of ibrutinib compared with existing WM therapies and in the modelling of pre-progression mortality. The committee heard from the ERG that their amended base-case ICER (including re-estimating drug acquisition and administration costs, correcting errors on follow-up costs and using pre-progression mortality data from PCYC-1118E) was between £56,000 and £57,000 per QALY gained when incorporating the updated PAS. The committee concluded that this was substantially above the range normally considered a cost-effective use of NHS resources (that is, between £20,000 and £30,000 per QALY gained).

5.1.6 Cancer Drugs Fund

Given that the uncertainty in the clinical and cost-effectiveness data was too great to recommend ibrutinib for routine use, the committee considered whether it would be appropriate to recommend ibrutinib for inclusion in the CDF. The committee can consider a recommendation for use within CDF if it is possible that the clinical uncertainty can be addressed through collection of outcomes data from patients treated in the NHS and, if the ICERs presented have the plausible potential to be cost-effective.

The committee considered what additional data could be collected to resolve some of the clinical uncertainties it had highlighted. The committee expressed interest in seeing updated efficacy data from the iNNOVATE trial and Study 1118E. The committee agreed that uncertainty in pre-progression mortality for those receiving ibrutinib could be addressed by collecting overall survival data using the Systemic Anti-Cancer Therapy dataset. The committee understood that the company intended to add-on to an existing national registry of people with WM to collect additional efficacy and resource use data. The committee heard from the clinical experts that the national registry includes over 300 patients and can record patient-level data (on progression, survival, response, quality of life, and genomic

markers). The committee considered that these data would be a valuable addition to the clinical evidence base and may resolve some of the uncertainties identified.

The committee heard from the company that it had made an offer to provide ibrutinib at a price that resulted in ibrutinib being cost-effective within the CDF. The committee also heard that the company was committed to exploring mechanisms for providing ibrutinib at a cost-effective price when it is re-appraised by NICE upon its exit from the CDF. The committee concluded that it would be able to recommend ibrutinib as an option for use within the CDF for treating WM provided that a managed access agreement was in place that allowed ibrutinib to be used cost-effectively within the CDF.

6. Appraisal committee's key conclusion

The committee considered that the most plausible ICER is likely to be at least £54,100 per QALY gained and noted that this is substantially above the level considered to be a cost-effective use of NHS resources. However, the committee concluded that it would be able to recommend ibrutinib as an option for use within the CDF for treating WM provided that a managed access agreement was in place that allowed ibrutinib to be used cost-effectively within the CDF.

Author contributions

Christopher Carroll and Emma Simpson summarised and critiqued the clinical effectiveness data reported within the company's submission. Paul Tappenden and Praveen Thokala critiqued the health economic analysis submitted by the company. Ruth Wong critiqued the company's search strategies. John Stevens critiqued the statistical analysis contained within the company's submission. Josh Wright and Rebecca Auer provided clinical advice to the ERG throughout the project. This summary has not been externally reviewed by PharmacoEconomics.

Compliance with Ethical Standards

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Conflict of interest

Rebecca Auer acted as an advisor for Janssen for their submission to NICE and was paid a small advisory fee for this role. Since the completion of this appraisal, Rebecca Auer has received a grant for a clinical trial which is anticipated to begin in November 2018. Paul Tappenden, Christopher Carroll, John Stevens, Emma Simpson, Praveen Thokala, Ruth Wong and Josh Wright declare no conflicts of interest.

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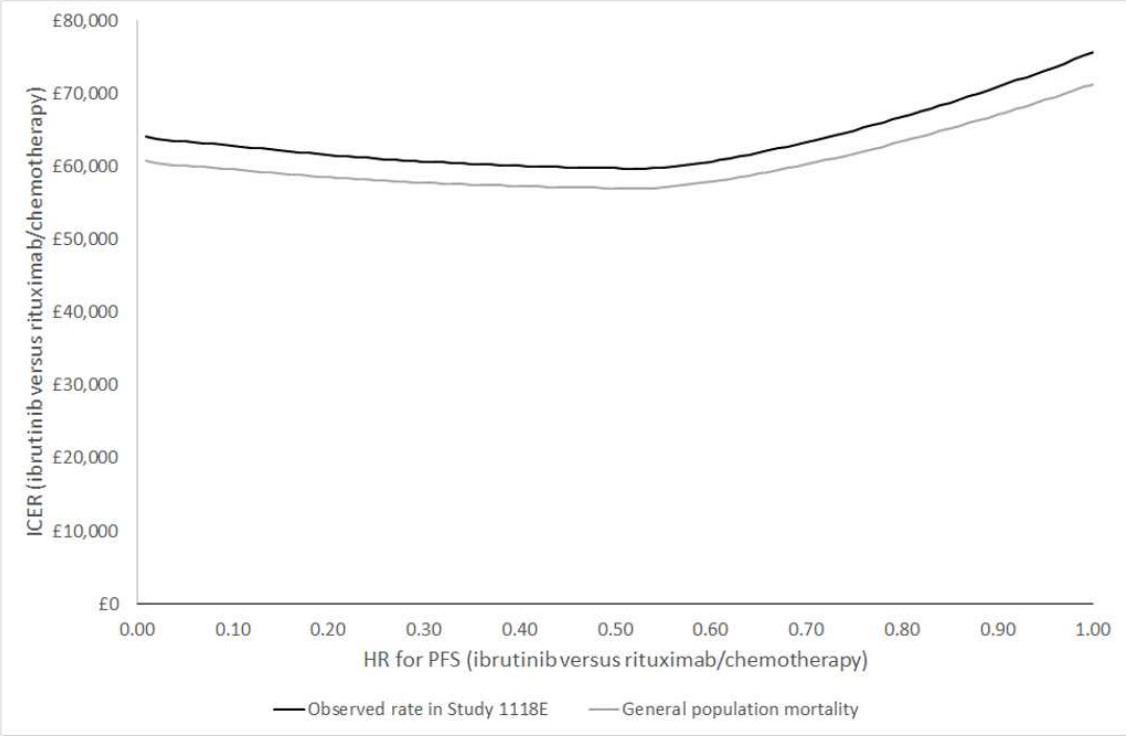
Table 1: Summary of evidence used to inform progression and death event rates by line of therapy

Model health state	Progression		Death	
	Ibrutinib	**Rituximab/chemotherapy**	**Ibrutinib**	**Rituximab/chemotherapy**
Second-line progression-free	Full population from Study 1118E (1-9 prior treatments). ERG comment Patients in the model by definition have only received one prior line of therapy on entry	Patients who had received between 1 and 4 prior lines of therapy in the ECR. ERG comment Patients in the model by definition have only received one prior line of therapy on entry	Based on life tables.	Patients receiving second-, third- or fourth-line therapy in the ECR. ERG comment Patients in the model by definition have only received one prior line of therapy on entry
Third-line progression-free	Patients starting fourth-line treatment in the ECR. ERG comment Patients in the model are by definition starting third-line treatment		Patients progressed from third-line treatment in the ECR. ERG comment Patients in the model are by definition progression-free in third-line	
Fourth-line progression-free	Patients starting fourth-line treatment in the ECR. ERG comment Evidence consistent with model		Patients progressed from third-line treatment in the ECR. ERG comment Evidence consistent with model	
BSC	Not applicable		Patients progressed from third-line treatment in the ECR. ERG comment Includes post-progression survival outcomes for patients receiving active therapy rather than BSC	

BSC – best supportive care; ERG – Evidence Review Group; ECR – European Chart Review

Figure 1: ERG exploratory analysis 10 - threshold analysis around HR for PFS (using the original PAS for ibrutinib in the WM indication). ICER incremental cost-effectiveness ratio, HR hazard ratio, PFS progression-free survival



HR – hazard ratio; PFS – progression-free survival; ICER – incremental cost-effectiveness ratio